Role of CYP1B1 in Glaucoma*

Vasilis Vasiliou[1] and Frank J. Gonzalez[2]

[1]Molecular Toxicology & Environmental Health Sciences Program, Department of Pharmaceutical Sciences, University of Colorado Health Sciences Center, Denver, Colorado 80262; email: vasilis.vasiliou@uchsc.edu

[2]Laboratory of Metabolism, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892; email: fjgonz@helix.nih.gov

Annu. Rev. Pharmacol. Toxicol. 2008. 48:333–58

First published online as a Review in Advance on October 3, 2007

The *Annual Review of Pharmacology and Toxicology* is online at http://pharmtox.annualreviews.org

This article's doi:
10.1146/annurev.pharmtox.48.061807.154729

0362-1642/08/0210-0333$20.00

Key Words

CYP, mutations, eye, transgenic mouse model, metabolism, steroids, arachidonic acid, retinoic acid, melatonin

Abstract

Glaucoma is a leading cause of blindness, estimated to affect 60 million people by 2010, and represents a heterogeneous group of neurodegenerative disease. The two major types of glaucoma include primary open-angle glaucoma (POAG) and primary congenital glaucoma (PCG). A genetically heterogeneous group of developmental disorders known as anterior segment dysgenesis (ASD) have been reported to be associated with increased intraocular pressure (IOP) and glaucoma. These include Peters' anomaly, Rieger's anomaly, aniridia, iris hypoplasia, and iridogoniodysgenesis. Genetic linkage analysis and mutation studies have identified CYP1B1 as a causative gene in PCG, as a modifier gene in POAG, and, on rare occasions, as causative gene in POAG as well as in several ASD disorders. CYP1B1-deficient mice exhibit abnormalities in their ocular drainage structure and trabecular meshwork that are similar to those reported in human PCG patients. Accordingly, it is speculated that diminished or absent metabolism of key endogenous CYP1B1 substrates adversely affects the development of the trabecular meshwork. CYP1B1 protein is involved in the metabolism of steroids, retinol and retinal, arachidonate, and melatonin. The conserved expression of CYP1B1 in both murine and human eyes, its higher expression in fetal than adult eyes, and its biochemical properties are consistent with this hypothesis. The exact role of CYP1B1 in the pathogenesis of glaucoma and other ASD disorders remains to be elucidated.

INTRODUCTION

Glaucoma is a leading cause of blindness. By 2010, glaucoma will affect an estimated 60 million people, and by 2020, that number is predicted to rise to 80 million (1). The glaucomas represent a heterogeneous group of complex neurodegenerative diseases, the common feature of which is gradual loss of vision. The neurodegeneration manifests as loss of retinal ganglion cells, characteristic changes in the visual field, and degeneration of the optic nerve (2). Elevated intraocular pressure (IOP) appears to be a major risk factor for glaucoma. A causal role of IOP has been clearly demonstrated in animals in which experimentally induced elevation of IOP causes glaucoma. Glaucomas may be categorized on the basis of etiology (primary and secondary), anatomy of the anterior chamber (open angle and closed angle), and the time of onset (infantile, juvenile, and adult). In general, glaucomas may be classified into three major categories: (*a*) primary open-angle glaucoma (POAG; OMIM 137760), (*b*) primary congenital glaucoma (PCG; OMIM 60975), and (*c*) primary angle closure glaucoma (PACG; no OMIM entry). In addition, a genetically heterogeneous group of developmental disorders known as anterior segment dysgenesis (ASD) have been reported to be associated with increased IOP and glaucoma (3). These include Peters' anomaly (PA; OMIM 604229), Rieger's anomaly (RA; OMIIM 180500 and 601499), aniridia (OMIM 106210), iris hypoplasia (OMIM 308500), and iridogoniodysgenesis (OMIM 137600).

The most common form of glaucoma is POAG and it affects more than 35 million people worldwide (1, 4). POAG is characterized by progressive cupping of the optic disc, with corresponding progressive visual field loss and, if untreated, eventual blindness. An increased frequency of the disease among relatives of POAG patients demonstrates that susceptibility is influenced by genetic factors. Cigarette smoking, diabetes, and myopia are also considered risk factors (5–7). Based on the age of onset, POAG is divided into juvenile-onset POAG (JOAG) and adult-onset POAG. JOAG (age of onset 3–35 years) is associated with high IOP, visual field loss, and optic disc damage and requires early surgical therapy (8, 9). It is typically inherited as an autosomal dominant trait, whereas adult-onset POAG is inherited as a complex trait (10). To date, 11 genetic loci for POAG have been identified (GLC1A–GLC1K; **Table 1**). However, only three causative genes have been described: *myocilin* (*MYOC/GLC1A*), *optineurin* (*OPTN/GLC1E*), and *WD repeat domain 36* (*WDR36/GLC1E*). Together, these account for less than 10% of POAG (11). A portion of POAG follows Mendelian inheritance and a considerable fraction results from a large number of variants in several genes, each contributing small effects (11). Mutations in *MYOC* account for approximately 2%–4% of POAG in Caucasians (12), 1.1%–1.8% in Chinese patients (13), and as high as 36% in JOAG families (14). Evidence for the causative effect of *OPTN*, arguably the second POAG gene, is somewhat controversial. Mutations in *OPTN* have been reported to occur in 17% of families with hereditary and adult-onset POAG and in 12% of sporadic patients with POAG, the majority of whom had an IOP of less than 22 mm Hg (15). Another study showed that *OPTN* mutations account for 1.6% of sporadic POAG in Chinese patients (16). In contrast, two recent studies investigating Caucasian POAG patients found no glaucoma-causing

Table 1 Genetic loci associated with glaucoma

	Locus	Chromosomal location	Gene	Reference
POAG	GLC1A	1q21-31	*MYOC*	(124)
	GLC1B	2cen-q13		(125)
	GLC1C	3q21-24		(126)
	GLC1D	8p23		(127)
	GLC1E	10p15-14	*OPTN*	(15)
	GLC1F	7q35-q36		(128)
	GLC1G	5q22.1	*WDR36*	(20)
	GLC1H	2p16.3-p15		(129)
	GLC1I	15q11-q13		(130)
	GLC1J	9q22		(131)
	GLC1K	20p12		(131)
	GLC1L	3p22-p21		(146)
	GLC1M	5q		(147)
	GLC1N	15q22-q24		(148)
PCG	GLC3A	2p21	*CYP1B1*	(30)
	GCL3B	1p36		(31)
	GLC3C	14q24.3-q31.1		(34)

mutations in *OPTN* (17, 18). Similarly, no specific glaucoma-causing *OPTN* mutations were identified in 148 Japanese patients with normal-tension glaucoma and 165 with high-tension glaucoma (19). The third gene for POAG was characterized as *WDR36* at *GLC1G* (20), and four mutations have been found to be associated with more than 5% of all sporadic cases of POAG (20).

Association studies have suggested that, in addition to causative genes, there are at least 16 POAG-associated genes (11). Most of these genes have been reported in single studies; a few of them have been investigated in multiple association studies, the findings of which are inconsistent. POAG-associated genes include apolipoprotein E (*APOE*; a potent modifier for POAG) (21), optic atrophy P (*OAP1*) (22), tumor protein p53 (*TP53*), tumor necrosis factor (TNF; reported to be associated with POAG in Chinese individuals) (23, 24) and cytochrome P450 1B1 (CYP1B1). CYP1B1 was initially suggested to be a modifier gene for the expression of MYOC in JOAG patients (25). However, recent studies have indicated that CYP1B1 may play an important role in JOAG, with possible monogeneic association in French (26), Indian (27), and Spanish (28) patients. Furthermore, mutations in CYP1B1 have been proposed as potential factors governing severity in POAG patients (29).

CYP1B1 has also been identified as one of the three genetic loci linked to PCG (**Table 1**) (30). The other two are GLC3B at chromosome locus 1p36 (31) and GLC3C at chromosome locus 14q24.3-q31.1 (32). Specific genes have not been

linked yet to the GLC3B and GLC3C loci. PCG is a form of glaucoma commonly referred to as infantile or congenital glaucoma. Although normally rare, it is the most common form of glaucoma in infants, with more than 80% of cases observed within the first year of life. This disorder is most likely due to developmental defects in the trabecular meshwork and the anterior chamber angle. The clinical findings in PCG patients typically include epiphora (watery eye), photophobia, corneal edema, and buphthalmolos (enlargement of the globe), which result from increased IOP. In PCG, elevated IOPs can rapidly lead to axonal loss and permanent loss of vision in untreated individuals. Sixty to eighty percent of cases involve both eyes, and males are more frequently affected than females (65% versus 35%, respectively). Inheritance is primarily autosomal recessive with variable penetrance (33). Ninety percent of cases are sporadic and pseudodominant transmission has been demonstrated in some families (30). Prevalence of PCG varies geographically from a rate of 1:10000 in Western countries (34) to 1:1250 in the Romany population of Slovakia (35).

CYP1B1 MUTATIONS IN GLAUCOMA

CYP1B1 is a member of the CYP450 superfamily that contains 58 and 102 putatively functional genes in the human and mouse genome, respectively (36). The human *CYP1B1* gene consists of three exons and two introns and spans 8.5 kb of genomic DNA (GenBank accession no. U56438). CYP1B1 was the first gene in the CYP450 gene superfamily in which a mutation was demonstrated to be involved in a primary developmental defect. The CYP1B1 gene is expressed in several tissues, including the eye, as well as in the nucleus of several cell types, including tubule cells of the kidney and secretory cells of the breast (37). The CYP1B1 gene product is a 543-amino acid-long protein that contains (*a*) a membrane-bound N-terminal region consisting of 53 residues; (*b*) a so-called hinge, which is a 10-residue-long proline-rich region; and (*c*) a cytosolic globular domain comprising 480 amino acids.

Table 2 lists the 82 mutations that have been identified in PCG, PA, RA, and POAG patients. These include 46 missense and 10 nosense mutations, 16 deletions, 8 insertions and/or duplications, and 2 silent mutations. The fact that approximately one-third of the mutations are genetic insertions or deletions indicates that *CYP1B1* is relatively susceptible to recombination events. The observation that mutations are found in patients with POAG, PA, and RA indicates that CYP1B1 mutations are associated with a broader range of clinical phenotypes than originally thought. CYP1B1 was initially identified by genetic linkage analysis and mutation screening as one of the loci GLC3A associated with PCG (38). Recent studies indicate a causative role of CYP1B1 in Peters' anomaly (39, 40). Specifically, four point mutations (W57X, M1T, P118T, and R368H) and a deletion (g.7899_7910del; R355-A358del) have been identified in patients with this condition (39–41). Additional evidence that CYP1B1 may be implicated in a pathophysiological mechanism common to PCG and other anterior dysgenesis disorders comes from a recent study showing that patients with Rieger's anomaly carry mutations in the CYP1B1 gene (W57X, g.4832_4834del, g.4838_4840del, and g.8037_8046dup) (42, 43). Finally, in certain pedigrees, both

Table 2 Mutations in the CYP1B1 gene detected in individuals with glaucoma and/or anterior segment dysgenesis. Nucleotides are numbered according to the CYP1B1 gene sequence listed in GenBank (accession number U56438)

Type of mutation	Exon	Nucleotide change	Protein change	Pathology	Origin (Reference)
Missense	2	g.3807T→C	M1T	PA*	Canadian (39)
	2	g.3888C→G	S28W	POAG	Spain (28)
	2	g.3947C→G	R48G	PCG	Saudi Arabia (33), Indian (44), Japan (132)
	2	g.3976G→C	W57C	PCG, POAG	Hispanic (48), India (27)
	2	g.3987G→A	G61E	PCG, POAG	Turkey (48), Saudi Arabia (133), Kuwait (134), Spain (28)
	2	g.4035T→C	L77P	PCG	Saudi Arabia (33)
	2	g.4046T→A	Y81N	POAG	French (26), Spain (28)
	2	g.4155G→C	R117P	PCG	Asian (135)
	2	g.4157C→A	P118T	PA/no PCG	Caucasian (40)
	2	g.4160G→T	A119S	PCG	Saudi Arabia (33), Japan (49)
	2	g.4237G→T	Q144H	POAG	Spain (28)
	2	g.4238C→T	R145W	POAG	Spain (28)
	2	g.4370G→C	A189P	OHT	Spain (28)
	2	g.4380A→T	D192V	PCG	Japan (49)
	2	g.4383C→T	P193L	PCG	Indian (44)
	2	g.4397G→A	V198I	PCG	Japan (49)
	2	g.4430T→C	C209R	PCG	Hispanic (135)
	2	g.4449G→T	S215I	PCG	Indonesia (41)
	2	g.4490G→A	E229K	PCG, POAG	Lebanon (136), Indian (44), France (26), India (27), Spain (28)
	2	g.4499G→C	G232R	PCG	France (137)
	2	g.4763G→T	V320L	PCG	Japan (49)
	2	g.4793G→T g.4794C→T	A330F	PCG	Japan (49)
	2	g.4793G→T	A330S	OHT	Spain (28)
	2	g.4838C→T	L345F	PCG	African American (25)
	3	g.7927G→A	V364M	PCG	Japan (49, 138)
	3	g.7930G→T	G365W	PCG	USA (48)
	3	g.7940G→A	R368H	PCG, PA, POAG	Saudi Arabia (33), Indian (44), Brazil (139), Kuwait (134), unknown (40), India (27)
	3	g.7957G→A	D374N	PCG	
	3	g.7983C→T	P379L	PCG	Turkey (48)
	3	g.7996G→A	E387K	PCG	Slovaks (140), Brazil (139), US, Canada, Romany
	3	g.7999G→A	A388T	PCG	Kuwait (134)
	3	g.8005C→T	R390C	PCG	Ecuador (141), Indian (142)
	3	g.8005C→A	R390S	PCG	Saudi Arabia (33)
	3	g.8006G→A	R390H	PCG, POAG	Pakistani (48), France (26)
	3	g.8033T→G	I399S	PCG	France (137)
	3	g.8062G→T	V409F	POAG	Spain (28)
	3	g.8104A→T	N423Y	PCG	France (137)
	3	g.8131G→C	L432V	PCG, PA	Turkey (30), Japan (49, 132)

(*Continued*)

Table 2 (*Continued*)

Type of mutation	Exon	Nucleotide change	Protein change	Pathology	Origin (Reference)
	3	g.8147C→T	P437L	PCG	Brazil (139)
	3	g.8165C→G	A443G	PCG, POAG, OHT	Brazil (139), France (26), Spain (28)
	3	g.8168G→A	R444Q	PCG	Japan (49)
	3	g.8242C→T	R469W	PCG	Saudi Arabia (133)
	3	g.8333A→G	E499G	PCG	Japan (49)
	3	g.8381C→T	S515L	POAG	India (27)
	3	g.8405G→C	R523T	POAG	India (27)
	3	g.8426A→G	D530G	POAG	India (27)
Nonsense	2	g.3860C→T	Q19X	PCG	Brazil (139)
	2	g.3929C→T	Q42X	PCG	Germany (43)
	2	g.3976G→A	W57X	PA, PCG, RA	Canada (39), Brazil (139), unknown (42)
	2	g.4547C→T	Q248X	PCG	France (137)
	2	g.4645C→A	C280X	PCG	Japan (49), Kuwait (134)
	2	g.4646G→T	G281X	PCG	Turkey (48)
	3	g.7900C→T	R355X	PCG	Turkey (136)
	3	g8104A→T	N423Y	POAG	France (26)
	3	g.8139G→A	W434X	PCG	Germany (43)
	3	g.8167C→T	R444X	PCG	France (137)
Deletions	2	g.3964delC	fs	PCG	Japan (49)
	2	g.3979delA	fs and 59X	PCG, POAG	France (137), France (26)
	2	g.4238_4247del	fs	PCG	Saudi Arabia (33)
	2	g.4081delC	fs	PCG	Turkey (136)
	2	g.4339delG	fs	PCG	Morocco (143)
	2	g.4340delG	51X	PCG	Brazil (139), Ecuador (141)
	2	g.4356delG	A179R/X 17 aa downstream	PCG	Mexico (144)
	2	g.4611_4619del	S268_F270del	PCG, POAG	Saudi Arabia (33), France (137), USA (145), France (26)
	2	g.4635delT	L277X	PCG	Mexico (144)
	2	g.4832_4834del	fs	RA	Germany (43)
	2	g.4838_4840del	L345del	RA	Unknown (42)
		g.7899_7910del	R355-A358del	PA	Turkey (41)
	3	g.7901_7913del	fs and 422X	PCG, POAG	Turkey (30), Brazil (139), France (26)
	3	G7945delC	P370L / X 57 aa downstream	PCG	Mexico (144)
	3	g.8182delG		PCG	Hispanic (48), Brazil (139), USA (48)
	3	g.8214_8215del	fs	PCG	Brazil (139)
Insertions and duplications	2	g.3835insA	223X		Indian (44)
	2	g.3956insC	fs	PCG	Russia (43)
	2	g.4306insT	fs	PCG	Turkey (48)
	2	g.4673insC	fs	PCG	Turkey (48)
	2	g.4776insAT	fs	PCG	Japan (49)
	3	g.8037_8046dup	fs	PCG, RA	Brazil (139); USA, Britain, Turkey (48); Germany (136), unknown (42)

(*Continued*)

Table 2 (*Continued*)

Type of mutation	Exon	Nucleotide change	Protein change	Pathology	Origin (Reference)
	3	g.8039_8048	T404S / X26 aa downstream	PCG	Mexico (144)
	3	g.8240_8266dup	fs	PCG	Turkey (48)
Silent	3	g.4534G→C	V243V	PCG	Japan (49)
	3	g.8184T→C	D449D	PCG	Japan (49)

*Abbreviations: PA, Peters' anomaly; POAG, primary open angle glaucoma; PCG, primary congenital glaucoma; RA, Rieger's anomaly; OHT, ocular hypertension; X, stop codon.

PCG and POAG segregate, indicating that that these two forms of glaucoma may also have a common or overlapping CYP1B1-mediated pathophysiological mechanism. Recent studies have shown mutations and coexistence of PCG and POAG in the same pedigree (44, 45). Moreover, a digenic inheritance of CYP1B1 and MYOC mutations have been shown to result in a phenotype with more pronounced glaucoma, suggesting that *CYP1B1* may function as a gene modifier for the *MYOC* gene (25). Interestingly, 11 of 236 unrelated French Caucasian POAG patients carried mutations in CYP1B1 but not in the MYOC gene. These individuals expressed juvenile or middle-age onset of the disease at a time significantly earlier than that in the noncarrier patients (26). With the exception of one silent mutation, all of these mutations have also been detected in PCG patients. A recent study in an Indian population revealed 6 CYP1B1 mutations in 9 of 200 POAG patients (27). Among these mutations, one novel homozygous mutation (R523T) was found, three were identical to those previously reported in PCG patients (W57C, E229K, and R368H), and two novel mutations (S515L and D530G) were detected in the heterozygous state (27). The R523T was detected in a familial juvenile onset POAG patient (lacking *MYOC* or *OPTN* mutations) and cosegregated with the disease locus in an autosomal recessive mode of transmission. All novel mutations detected in this study (R523T, S515L, and D530G) were found in a *CYP1B1* region that does not harbor any of the missense mutations implicated in PCG or other anterior segment dysgenesis disorders (27). Collectively, these studies suggest that *CYP1B1* may have a larger role than initially thought in glaucoma pathogenesis, ranging from a causal effect in PCG and other anterior segment dysgenesis disorders, to modifying the pathogenesis of POAG or being the primary cause of JOAG under some circumstances.

The crystal structure of CYP1B1 has not yet been determined, although it can be predicted based on conserved sequences found in many P450s (46, 47). Such comparative modeling predicts that missense mutations in CYP1B1 would affect elements that coincide with highly conserved and functionally important regions of the P450 enzyme. For example, mutations associated with W57C, G61E, G365W, P379L, R390H, E387K, P437L, and R469W might disrupt either the hinge region or the conserved core of the protein (48). Another study suggested that one (R444Q) out of the four (D192V, A330F, V364M, and R444Q) missense mutations in CYP1B1 protein could cause significant structural changes (49). In a recent study, wild-type

and the mutant model structures corresponding to the eight PCG mutations (A115P, M132R, Q144P, P193L, E229K, S239R, R368H, and G466D) were developed for the application of comparative modeling approaches (47). These models were subjected to molecular dynamics simulations for studying the time evolution as well as time-averaged values of structural properties with emphasis on the functionally important regions. The results of these simulations indicated that the mutant structures exhibit properties that may not be conducive to enzymatic function (47).

EXPRESSION OF CYP1B1 IN THE EYE

Expression of CYP1B1 has been studied in both human and mouse eyes. In the human eye, CYP1B1 mRNA has been detected in relatively high levels in the iris and ciliary body and in lower levels in the cornea, retinal-pigment epithelium, and retina (48). Interestingly, immunohistochemical analyses revealed an absence of CYP1B1 protein expression in the trabecular meshwork of human fetal and adult eyes (50); however, it was demonstrated in nonpigmented ciliary epithelium, corneal epithelium and keratocytes, both layers of the iris pigmented epithelium, and retina (48). Differences exist between adult and fetal eyes; for example CYP1B1 immunostaining in fetal eyes was more intense than that observed in adult eyes. CYP1B1 mRNA was not among the transcripts expressed in infant human trabecular meshwork (51). By contrast, CYP1B1 transcripts were detected in an adult human trabecular meshwork cDNA library, although CYP1B1 was not among the 50 most abundant cDNA clones (52). CYP1B1 mRNA was also detected in the trabecular meshwork by semiquantitative RT-PCR amplification (48).

A similar pattern of CYP1B1 protein expression was observed in the eyes of adult C57BL/6 mice, with the protein being found in the corneal epithelium, inner ciliary epithelial cells, retinal ganglion cells, and inner nuclear layers and with trace expression in the lens epithelium (53). By contrast, structures derived from the periocular mesenchyme, such as iris, corneal stroma, or outer ciliary epithelium, did not express the CYP1B1 protein (53) despite CYP1B1 mRNA having been detected in the outer ciliary epithelium from P4 through adulthood in the eyes of FVB/N mice (54). A recent study showed that CYP1B1 is expressed in endodermal, mesodermal, and ectodermal derivatives during chick embryo development, including in the anterior segment of the eye and anterior retina (55).

The conserved expression of CYP1B1 in both murine and human eyes, together with the observation that this protein is differentially distributed throughout the eye and found in higher levels in fetal than adult eyes, is consistent with a role for it in ocular function and/or development. Diminished or absent metabolism of important endogenous substrates in the ciliary epithelium as a consequence of altered CYP1B1 could contribute to developmental defects leading to eye pathophysiologies. The ciliary body is the primary source of aqueous humor generation and is involved in the production of mediators that modulate extracellular matrix turnover by secreting metalloproteases (56). Accordingly, mutations in genes expressed by the ciliary body may directly contribute to an abnormal elevation in IOP or indirectly affect the aqueous outflow by disrupting the proper development of trabecular meshwork

in glaucoma patients. By metabolizing ciliary body-derived mediators involved in these processes, CYP1B1 could influence IOP. Consistent with this proposal is the recent study linking CYP1B1 with early-onset POAG in French and Indian patients (27).

Cyp1b1-NULL MICE

To study the role of CYP1B1 in glaucoma, transgenic knockout *Cyp1b1(–/–)* mice on a mixed 129 × 1/SvJ X C57BL/6J background were generated (57). Gross examination of eyes from these mice revealed normal-appearing anterior segments and no apparent evidence of glaucoma. The animals were not blind, as determined by standard behavioral comparisons with their wild-type littermates, in their response to light and dark (57). Further studies confirmed the absence of gross abnormalities in *Cyp1b1(–/–)* mice up to the age of 13 months and that their intraocular pressures were indistinguishable from those of their wild-type littermates (58). However, electron microscopy of the anterior eye segment revealed that *Cyp1b1(–/–)* mice had abnormalities in their ocular drainage structure that resembled those reported for human PCG patients (58). Such abnormalities included hypoplastic trabecular meshwork, abnormally located basal lamina in the trabecular meshwork, and iridocorneal adhesions. Although these abnormalities were not associated with increased IOP (58), recent reports indicate that *Cyp1b1*-null mice have some elevation in IOP (53). Further studies are needed to examine the IOP in these transgenic knockout mice.

Crossing the *Cyp1b1* mutation onto a tyrosinase-deficient background (129 × 1/SvJ) resulted in more severe iridocorneal angle abnormalities, suggesting that the tyrosinase (*TYR*) may serve as a modifier gene of iridocorneal angle defects (58). TYR is a multifunctional copper-containing glycoenzyme that plays a pivotal role in the rate-limiting steps of the melanin synthesis, making *Tyr*-deficient mice albino. The contribution of TYR in iridocorneal angle abnormalities is further supported by the increased incidence of ASD in people with albinism (59). Interestingly, it has been found that *Tyr* also modifies iridocorneal angle phenotypes in another mouse model of ASD, (*Foxc1* +/–) mice, suggesting that the effect of *Tyr* may not be specific to CYP1B1 deficiency. However, a recent genome-wide single-nucleotide polymorphism (SNP) analysis in the TYR chromosomal region 11q13-q21 and sequencing of the TYR gene suggested that TYR is not a modifier of the CYP1B1-associated PCG phenotype in the Saudi Arabian population (60). In addition, Bejjani and colleagues have suggested the existence of a dominant suppressor of the PCG phenotype that is not genetically linked to CYP1B1 (33). The iridocorneal abnormalities observed in *Cyp1b1(–/–)/Tyr(–/–)* double mutant mice were alleviated (but not rescued) after treatment with the tyrosinase product, dihydroxyphenylalanine (L-dopa) (58). Therefore, it has been concluded that tyrosine hydroxylase, which produces L-dopa from tyrosine, could act as another such modifying factor. In addition, it has been proposed that CYP1B1 may affect tyrosine hydroxylase expression by producing retinoids that promote proliferation of neural crest cells expressing tyrosine hydroxylase (50). Development of the *Cyp1b1*-null mice along with the CYP1B1 humanized mice should help to elucidate the molecular mechanisms underlying glaucoma.

FUNCTIONS OF CYP1B1

CYP1B1 is a dioxin-inducible gene and a member of the AHR gene battery that is involved in the metabolism of both endogenous and exogenous substrates (61). It is involved in the metabolism of carcinogens, as well as in the synthesis of steroid hormones and other lipid molecules that can act in signal transduction pathways that regulate the differentiation and growth of tissues. Through such mechanisms, CYP1B1 may be involved in early ocular differentiation. Among the carcinogens metabolized by CYP1B1 are polycyclic aromatic hydrocarbons, many *N*-heterocyclic amines, arylamines, amino azo dyes, and several other carcinogens (62). Endogenous compounds susceptible to CYP1B1 include steroids, retinoic acid (RA), and melatonin.

STEROID METABOLISM

The recent observation that early menopause in women is associated with an increased risk for open-angle glaucoma suggests that endogenous steroids may be involved in the pathogenesis of glaucoma (63). Testosterone and estradiol are ligands for the cytoplasmic androgen receptors and nuclear estrogen receptors, respectively. Ligand-activated receptors transcriptionally regulate a number of genes (including CYP1B1) through binding to DNA response elements in the promoter region of these genes. As mentioned earlier, CYP1B1 is a proposed modifier for MYOC in patients with POAG. MYOC is inducible by administration of the steroid, dexamethasone (64). It is therefore plausible that a metabolic-impaired CYP1B1 in glaucoma patients may further compromise the function of the mutant MYOC protein, with a subsequent manifestation of the disease at an earlier age (25). This is in agreement with the proposal that open-angle glaucoma may not be a monogenic disease (65). Functional interactions between CYP1B1 and MYOC have not yet been investigated. Human CYP1B1 metabolizes testosterone relatively poorly but is much more effective in metabolizing estradiol (66). Metabolism of estradiol by CYP1B1 generates several metabolites, including the catechol estrogens, 4-OH-estradiol and 2-OH-estradiol (which account for the 75%–80% of the metabolites), the B-ring metabolites 6α- and 6β-OH estradiol, and D-ring 15 α-and 16 α-OH estradiol metabolites (**Figure 1**) (66). The 4-OH metabolite appears to be the major product formed by CYP1B1 (67). The effects of two CYP1B1 mutations (G61E and R469W) found in PCG patients have been studied recently by expressing the mutant proteins in *Escherichia coli* (66). The G61E protein showed diminished stability and the R469W holoenzyme had stability similar to CYP1B1. Both mutants showed compromised catalytic activity toward testosterone, progesterone, and estradiol, supporting the notion that CYP1B1 is necessary for normal embryonic or fetal tissue development. In addition to the mutations identified in PCG, POAG, and other ASD disorders, several polymorphisms of CTP1B1 have been described (**http://www.cypalleles.ki.se/cyp1b1.htm**). The CYP1B1*3 allele (L432V) is associated with first trimester miscarriage, possibly through the involvement of CYP1B1 in the metabolism of estradiol and testosterone (68). Studies with recombinant

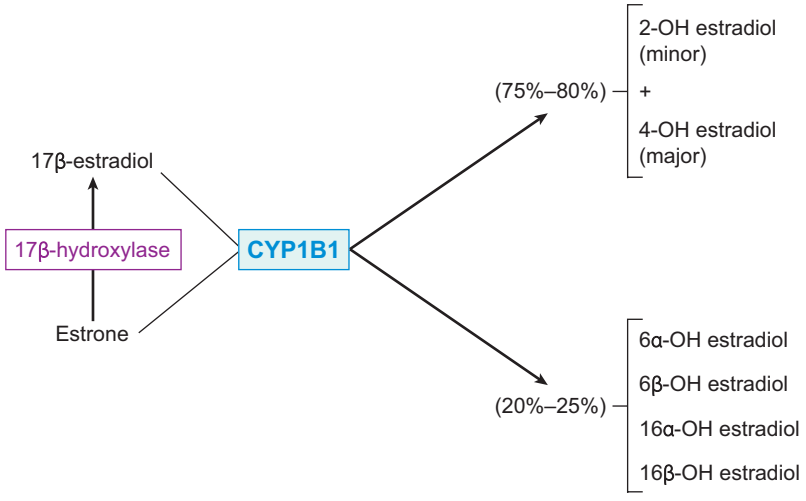

Figure 1

Role of CYP1B1 in estradiol metabolism (adapted from Reference 123). 17β-estradiol is converted to several hydroxylated metabolites by CYP1B1, the majority of which are the 2-OH and 4-OH derivatives, also referred to as catechol estrogens.

proteins have shown that CYP1B1.3 variants catalyze 17b-estradiol 4-hydroxylation at a K_m that is 4.5-fold lower than the wild-type CYP1B1*1 (Leu432) variant (69). Furthermore, the CYP1B1.1 (wild-type) protein has been shown to catalyze testosterone 6-hydroxylation at a V_{max}/K_m ratio that is 3.3- to 6.5-fold higher than that of the CYP1B1*3 (70). The CYP1B1*1/1*1 genotype seems to be associated with an increased breast cancer risk (71), whereas the CYP1B1*3/1*3 genotype has been associated with estrogen and P receptor–positive status in breast cancer in Caucasians (72).

Arachidonic Acid Metabolism

Arachidonic acid is a free fatty acid that, when liberated from cell membranes, can be metabolized by cyclooxygenases (COXs), lipoxygenases (LOs), and CYP450s to biologically active products, such as prostaglandins, leukotrienes, epoxyeicosatrienoic acids, and hydroxyeicosatetraenoic acids (73). The hydroxyl derivatives can be further divided into three classes, depending on the site of oxidation, e.g., terminal, midchain, or bisallylic sites (74). Arachidonic acid metabolites are very potent molecules with angiogenic, chemotactic, and migratory activities (53, 75). 12(R)-hydroxyeicosatetraenoic acid [12(R)HETE] is a corneal epithelial arachidonic acid metabolite formed by the CYP450 system that has been shown to be a potent inhibitor of Na^+-K^+ (+)-ATPase activity (76). The latter regulates corneal transparency (77). Modulation of this ATPase activity affects corneal susceptibility to pressure-induced hydration, which promotes the corneal clouding associated with glaucoma. On the other hand, 12(R)HETE has been shown to lower IOP in rabbits (78). The role of CYP1A1, CYP1A2, and CYP1B1 in arachidonate metabolism was recently studied using human and mouse proteins (74). The profile of arachidonic acid metabolites formed by CYP1B1 differs significantly from those generated by CYP1A1 and CYP1A2. Specifically, CYP1A1 primarily produced terminal ω-hydroxy metabolites

(terminal HETEs), CYP1A2 generated more epoxy products (EETs), and CYP1B1 formed mostly midchain HETEs (74). Murine CYP1B1 only poorly metabolizes arachidonate (K_m of 0.5 mM and a very low V_{max} activity) to the extent that its catalytic efficiency for arachidonate is only 2% of human CYP1B1 (53). These catalytic differences between human and mouse CYP1B1 proteins suggest that arachidonate might not be a conserved substrate involved in the pathogenesis of PCG, POAG, and other ASD disorders.

Retinol and Retinal Metabolism

RA is a pleiotrophic regulator of morphogenesis and differentiation, providing positional information to cells as they develop during embryogenesis and as they are regenerated in adult tissues. RA is formed from vitamin A (retinol) in a two-step metabolic pathway in which retinol is first oxidized to retinaldehyde, and then retinaldehyde is oxidized to RA (79). RA functions as a ligand for retinoid signaling events that directly regulate gene expression (79). It is well known that retinoid signaling mediates embryonic pattern formation during development of several organs such as eye, limb buds, hindbrain, and spinal cord (80). It is also well known that either an excess or a deficiency of vitamin A and related compounds (retinoids) is associated with teratogenesis and death. Vitamin A deficiency is characterized by a number of teratologies, including severe malformations of the developing CNS and cardiovascular system, face, and eyes that may ultimately lead to embryonic death (81, 82). In addition, excess of retinoids cause teratogenesis associated with craniofacial malformations (83). Impaired retinoid homeostasis observed in aryl hydrocarbon receptor (AHR)-null mice is associated with liver fibrosis, which is prevented with a vitamin A–deficient diet in mice (84–86).

The synthesis and degradation of RA in vivo are tightly coupled. During development, RA is initially produced intracellularly by two oxidation reactions of the maternally derived retinol to retinal and then to RA. The first oxidation is catalyzed by retinol and alcohol dehydrogenases and the second step by aldehyde dehydrogenases (ALDH1A1/A2/A3 and ALDH8A1) (**Figure 2**) (79). Following binding to RA-binding protein (CRABP) in the cytosol, RA translocates to the nucleus and binds to the nuclear RA receptors (RARs) and retinoid X receptors (RXRs), which are ligand-dependent transcriptional regulators. The RA-RAR-RXR complex modulates expression of targeted genes via RA response elements (RAREs). In the recent years CYP450s have also been suggested to be involved in the synthesis and degradation of RA (74, 55). RA can be further oxidized by CYP26A1/B1/C1 to 4-*oxo*-RA, 4-OH-RA and 5,8-*epoxy*-RA. Although it was initially proposed that these RA metabolites are biologically inactive (87), recent studies indicate that these metabolites have signaling properties (88). In addition to CYP26 enzymes, CYP1B1 is also capable of metabolizing retinoids. Studies with mouse and human CYP1B1 proteins showed that these proteins oxidize all-*trans*-retinol to all-*trans*-retinal, and all-*trans*-retinal to all-*trans*-RA (74). This study also showed that the human enzyme has a considerably lower K_m for retinol and retinal than the mouse enzyme. However, mouse CYP1B1 exhibits a V_{max} for retinol oxidation to retinal, which is two-fold of that of the human enzyme

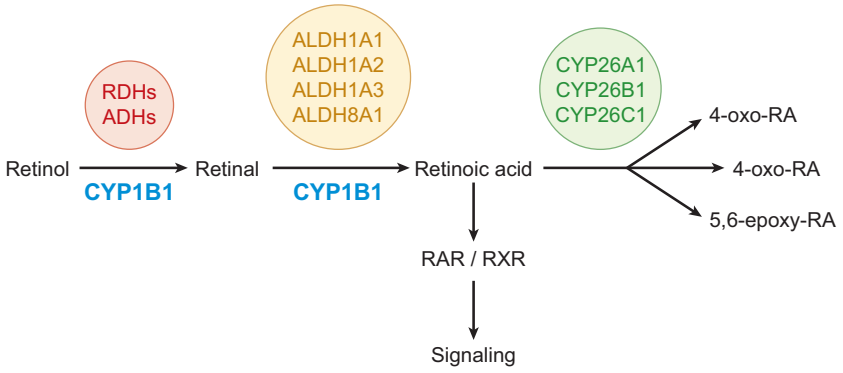

Figure 2

Metabolism of retinol, retinal, and retinoic acid. Retinaldehyde dehydrogenase (RDH) and alcohol dehydrogenase (ADH) can convert retinol to retinal, respectively, the latter of which is converted to retinoic acid by several aldehyde dehydrogenases (ALDH). CYP1B1 is also capable of carrying out these reactions. However, in the presence of RDH, ADH, and ALDH in a particular cell type, its contribution would not be significant. Retinoic acid is the main signaling molecule, as it is the primary ligand for the retinoic acid receptors. Retinoic acid is inactivated by CYP26 CYP450s.

and similar to the human enzyme for the oxidation of retinal to RA. These data led the authors to suggest that at physiological levels of vitamin A both enzymes may contribute to RA formation. On the other hand, neither human or mouse CYP1B1 was found capable of oxidizing RA. Similar data regarding human CYP1B1 have been recently published along with the observation that CYP1B1 and ALDHs may complement each other in the production of RA, with the CYP1B1 providing retinal to the ALDHs and contributing to the formation of RA (55). The authors also proposed that CYP1B1 could be the only enzyme generating RA in tissues in which ALDHs are not expressed (55). In conclusion, it is possible that CYP1B1 is involved in the formation of RA; however, in vivo experiments are needed to confirm this possibility.

Melatonin Metabolism

Melatonin (*N*-acetyl-5-methoxytryptamine) is an indoleamine neurohormone that is widely distributed in nature and found in bacteria, protozoa, plants, fungi, invertebrates, and vertebrates (89). In animals, circulating melatonin is mainly synthesized in the pineal gland; however, several tissues are capable of synthesizing melatonin, including bone marrow, gastrointestinal tract, skin, and eye (90). In the eye, melatonin synthesis occurs in the retina (91), lacrimar gland (92), lens (93, 94), and ciliary body (95). Retinal photoreceptors synthesize melatonin, which is rapidly metabolized in *Xenopus* retina, thus restricting its action to retina (96). The animal ciliary body synthesizes melatonin rhythmically and apparently secretes it into the aqueous humor (95, 97, 98). Melatonin found in aqueous humor parallels with the circadian rhythm of the plasma with peak levels occurring during the night cycle (95, 99, 100).

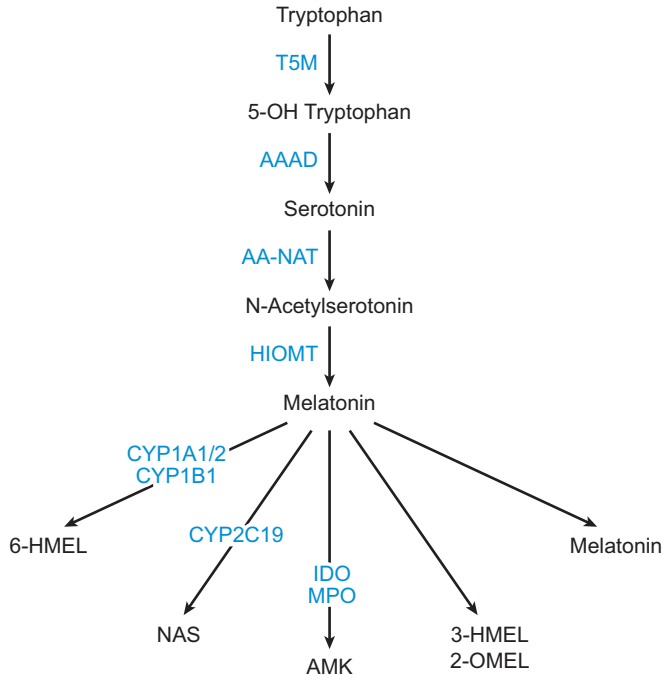

Figure 3

Melatonin synthesis and metabolism (modified from Reference 103). Tryptophan hydroxylation and subsequent decarboxylation forms serotonin (5-hydroxytryptamine). Sequential action of serotonin *N*-acetyltransferase (acetyl CoA: arylalkylamine *N*-acetyltransferase, EC 2.3.1.87; AA-NAT) and hydroxyindole-*O*-methyltransferase (*S*-adenosyl-methionine: *N*-acetylserotonin *O*-methyltransferase, EC 2.1.1.4; HIOMT) generate melatonin. Melatonin is catabolized primarily to 6-hydroxymelatonin (6-HMEL) by CYP1A1, CYP1A2, and CYP1B1 and to a minor metabolite N-acetyl-5 hydroxytryptamine (NAS) by CYP2C19. Oxidative metabolism catalyzed indoleamine-2,3-dioxygenase (IDO) and/or myeloperoxidase (MPO) leads to the formation of N^1-acetyl-N^2-formyl-5-methoxy-kynurenine (AFMK) and then N^1-acetyl-5-methoxy-kynurenine (AFK). *N*-[2-(5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-ethyl]-acetamide (2-OMEL) and cyclic 3-hydroxymelatonin (3-HMEL).

Melatonin is synthesized in a pathway that initially involves tryptophan hydroxylation and subsequent decarboxylation to form serotonin (5-hydroxytryptamine). Sequential action of serotonin *N*-acetyltransferase (acetyl CoA: arylalkylamine *N*-acetyltransferase, EC 2.3.1.87; AA-NAT) and hydroxyindole-*O*-methyltransferase (*S*-adenosyl-methionine: *N*-acetylserotonin *O*-methyltransferase, EC 2.1.1.4; HIOMT) (101, 102) lead to the formation of melatonin (**Figure 3**). The AA-NAT is, in most cases, the rate-limiting enzyme controlling melatonin synthesis (103).

Melatonin is metabolized primarily to 6-hydroxymelatonin (6-HMEL) by CYP1A1, CYP1A2, and CYP1B1, and to a minor metabolite N-acetyl-5 hydroxytryptamine (NAS) by CYP2C19 (104, 105). Oxidative metabolism catalyzed indoleamine-2,3-dioxygenase (IDO) and/or myeloperoxidase (MPO) leads to the

formation of N^1-acetyl-N^2-formyl-5-methoxy-kynurenine (AFMK), which is deformelated spontaneously or ezymatically by kynurerine formamidase to more stable N^1-acetyl-5-methoxy-kynurenine (AFK) (106–108). In addition, *N*-[2-(5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-ethyl]-acetamide (2-OMEL) and cyclic 3-hydroxymelatonin (3-HMEL) have been recently identified as oxidation metabolites (108).

In the eye, melatonin has a variety of biological effects modulating retinomotor movements (109), dopamine synthesis and release (110, 111), photoreceptor outer segment disc shedding (112), IOP (100), and, most importantly, ocular growth and development (113). The functions of melatonin are mediated by the melatonin receptors. Three melatonin receptors have been identified and include MT1 and MT2 receptors and the cytosolic enzyme quinone reductase 2 (QR2/MT3) involved in several metabolic processes (103). Melatonin receptors are found in the cornea, iris, sclera, choroid, photoreceptors, RCGs, and retinal blood vessels (114), as well as the iris-ciliary processes (115) and in the nonpigmented ciliary epithelium (116). The expression of melatonin receptor in the iris and ciliary processes has led to the hypothesis that these molecules are involved in the aqueous humor secretion and the circadian rhythm of IOP (115, 117). However, studies regarding the effect of melatonin on IOP have had conflicting results. Topically applied melatonin and the selective MT3 receptor agonist, 5-methoxycarbonylamino-N-acetyltryptamine (5-MCA-NAT), was found to significantly reduce IOP in rabbits, whereas the nonspecific melatonin receptor antagonist, luzindole, abolished the depressant effect of both compounds, supporting the involvement of melatonin receptors in the regulation of IOP (118). The same group found that topical administration of melatonin and its analogues, 2-Phe-melatonin, 6-Cl-melatonin, 2-I-melatonin, 5-MCA-NAT, and N-acetyltryptamine, caused a reduction in IOP (119). They also found that the melatonin-receptor antagonists, prazosin, DH-97, and 4-P-PDOT, reversed the effect of 5-MCA-NAT in a dose-dependent manner (119). The 5-MCA-NAT also reduced IOP in monkeys with laser-induced glaucoma (120). On the contrary, another study found that melatonin injected into the vortex vein of a rabbit eye produced an increase in IOP that lasted for up to 5 h. In addition, melatonin prevented haloperidol-induced decrease in IOP, most likely through physiological antagonism (121). Similarly, intracameral infusion of melatonin into cat eyes decreased aqueous humor synthesis but caused a greater decrease in aqueous humor outflow, which was associated with a significant increase in IOP (98). Individuals exposed to bright light for 23 h had reduced urinary 6-OH melatonin levels and an attenuated early-morning fall in IOP compared with those exposed in dim light (122). In addition, oral melatonin administration to subjects kept in bright light for 23 h caused a small but significant decrease in IOP (122). Further studies are needed to determine the role of melatonin in glaucoma.

CONCLUSIONS AND PERSPECTIVES

Recent studies have identified *CYP1B1* as a causative gene in PCG, as a modifier gene in POAG, and, rarely, as a causative gene in POAG and several ASD disorders. CYP1B1-deficient mice exhibit abnormalities of the ocular drainage structure similar

to those reported for human PCG patients. What is the role of CYP1B1 in glaucoma? The current hypothesis is that CYP1B1 metabolizes an endogenous substrate to generate a metabolite needed for development or eliminates a substrate that is crucial for development. As discussed above, CYP1B1 may be involved in the metabolism of steroids, arachidonic acid, vitamin A, and melatonin. All of these metabolic pathways could potentially generate signaling molecules that may be involved in the development and pathogenesis of glaucoma and other ASD disorders. However, the question that needs to be addressed is which of these pathways is causative and/or critical for these disorders. The existence of another CYP1B1-mediated pathway that may be involved in glaucoma also can not be ruled out. The extensive allelic heterogeneity of *CYP1B1* observed in glaucoma patients supports this hypothesis, and also raises the possibility that different mutations of this gene may result in variable levels of enzymatic activity or even altered substrate specificity. This may have an impact in the CYP1B1-mediated metabolism resulting in individual differences in the concentration of CYP1B1 metabolites and possibly to different phenotypes. Indeed, recent studies in geneotype (mutations in *CYP1B1*)-phenotype (degree of angle dysgenesis and disease severity) correlations in POCG patients indicated that specific *CYP1B1* mutations may be associated with severe or moderate angle abnormalities (149). Such studies may provide glaucoma specialists with the molecular tools that will assist in the diagnosis of PCG, including prenatal cases (151), the prediction of clinical course, and development of appropriate treatments (151). However, further studies are needed to determine the precise role of CYP1B1 in glaucoma and ASD disorders. The *Cyp1b1*-null mice provide an excellent experimental model for such studies. The hypothesis that CYP1B1 metabolizes an endogenous substrate to generate a metabolite crucial for development or eliminates a substrate that disrupts development can be elucidated using metabolomic approaches in aqueous humorous of wild-type and *Cyp1b1*-null mice. Furthermore, gene expression studies along with 2D gel analysis and proteomics in the anterior eye of these mice during development should reveal important information regarding the involvement of *CYP1B1* in the pathogenesis of glaucoma.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank Drs. David Thompson and John Danias for valuable discussions and critical review of this manuscript. This work was supported in part by National Institutes of Health grant EY11490.

LITERATURE CITED

1. Quigley HA, Broman AT. 2006. The number of people with glaucoma worldwide in 2010 and 2020. *Br. J. Ophthalmol.* 90:262–67

2. Weinreb RN, Khaw PT. 2004. Primary open-angle glaucoma. *Lancet* 363:1711–20
3. Gould DB, John SW. 2002. Anterior segment dysgenesis and the developmental glaucomas are complex traits. *Hum. Mol. Genet.* 11:1185–93
4. Fraser SG. 2004. Epidemiology of primary open angle glaucoma. In *Glaucoma*, ed. R Hitchings, pp. 9–15. London: BMJ Publ. Group
5. Bonovas S, Filioussi K, Tsantes A, Peponis V. 2004. Epidemiological association between cigarette smoking and primary open-angle glaucoma: a meta-analysis. *Pub. Health* 118:256–61
6. Bonovas S, Peponis V, Filioussi K. 2004. Diabetes mellitus as a risk factor for primary open-angle glaucoma: a meta-analysis. *Diabet. Med.* 21:609–14
7. Yoshida M, Okada E, Mizuki N, Kokaze A, Sekine Y, et al. 2001. Age-specific prevalence of open-angle glaucoma and its relationship to refraction among more than 60000 asymptomatic Japanese subjects. *J. Clin. Epidemiol.* 54:1151–58
8. Johnson AT, Richards JE, Boehnke M, Stringham HM, Herman SB, et al. 1996. Clinical phenotype of juvenile-onset primary open-angle glaucoma linked to chromosome 1q. *Ophthalmology* 103:808–14
9. Wiggs JL, Del Bono EA, Schuman JS, Hutchinson BT, Walton DS. 1995. Clinical features of five pedigrees genetically linked to the juvenile glaucoma locus on chromosome 1q21-q31. *Ophthalmology* 102:1782–89
10. Wiggs JL, Damji KF, Haines JL, Pericak-Vance MA, Allingham RR. 1996. The distinction between juvenile and adult-onset primary open-angle glaucoma. *Am. J. Hum. Genet.* 58:243–44
11. Fan BJ, Wang DY, Lam DSC, Pang CP. 2006. Gene mapping for primary open angle glaucoma. *Clin. Biochem.* 39:249–58
12. Fingert JH, Heon E, Liebmann JM, Yamamoto T, Craig JE, et al. 1999. Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. *Hum. Mol. Genet.* 8:899–905
13. Pang CP, Lam DSC. 2002. Differential occurrence of mutations causative of eye diseases in the Chinese population. *Hum. Mutat.* 19:189–208
14. Shimizu S, Lichter PR, Johnson AT, Zhou Z, Higashi M, et al. 2000. Age-dependent prevalence of mutations at the GLC1A locus in primary open-angle glaucoma. *Am. J. Ophthalmol.* 130:165–77
15. Rezaie T, Child A, Hitchings R, Brice G, Miller L, et al. 2002. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science* 295:1077–79
16. Leung YF, Fan BJ, Lam DSC, Lee WS, Tam POS, et al. 2003. Different optineurin mutation pattern in primary open-angle glaucoma. *Invest. Ophthalmol. Vis. Sci.* 44:3880–84
17. Alward WLM, Kwon YH, Kawase K, Craig JE, Hayreh SS, et al. 2003. Evaluation of optineurin sequence variations in 1048 patients with open-angle glaucoma. *Am. J. Ophthalmol.* 136:904–10
18. Wiggs JL, Auguste J, Allingham RR, Flor JD, Pericak-Vance MA, et al. 2003. Lack of association of mutations in optineurin with disease in patients with adult-onset primary open-angle glaucoma. *Arch. Ophthalmol.* 121:1181–83

19. Tang S, Toda Y, Kashiwagi K, Mabuchi F, Iijima H, et al. 2003. The association between Japanese primary open-angle glaucoma and normal tension glaucoma patients and the optineurin gene. *Hum. Genet.* 113:276–79
20. Monemi S, Spaeth G, DaSilva A, Popinchalk S, Ilitchev E, et al. 2005. Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5q22.1. *Hum. Mol. Genet.* 14:725–33
21. Copin B, Brezin AP, Valtot F, Dascotte JC, Bechetoille A, Garchon HJ. 2002. Apolipoprotein E-promoter single-nucleotide polymorphisms affect the phenotype of primary open-angle glaucoma and demonstrate interaction with the myocilin gene. *Am. J. Hum. Genet.* 70:1575–81
22. Powell BL, Toomes C, Scott S, Yeung A, Marchbank NJ, et al. 2003. Polymorphisms in OPA1 are associated with normal tension glaucoma. *Mol. Vis.* 9:460–64
23. Lin HJ, Chen WC, Tsai FJ, Tsai SW. 2002. Distributions of p53 codon 72 polymorphism in primary open angle glaucoma. *Br. J. Ophthalmol.* 86:767–70
24. Lin HJ, Tsai FJ, Chen WC, Shi YR, Hsu Y, Tsai SW. 2003. Association of tumour necrosis factor alpha –308 gene polymorphism with primary open-angle glaucoma in Chinese. *Eye* 17:31–34
25. Vincent AL, Billingsley G, Buys Y, Levin AV, Priston M, et al. 2002. Digenic inheritance of early-onset glaucoma: CYP1B1, a potential modifier gene. *Am. J. Hum. Genet.* 70:448–60
26. Melki R, Colomb E, Lefort N, Brezin AP, Garchon HJ. 2004. CYP1B1 mutations in French patients with early-onset primary open-angle glaucoma. *J. Med. Genet.* 41:647–51
27. Acharya M, Mookherjee S, Bhattacharjee A, Bandyopadhyay AK, Daulat Thakur SK, et al. 2006. Primary role of CYP1B1 in Indian juvenile-onset POAG patients. *Mol. Vis.* 12:399–404
28. Lopez-Garrido MP, Sanchez-Sanchez F, Lopez-Martinez F, Aroca-Aguilar JD, Blanco-Marchite C, et al. 2006. Heterozygous CYP1B1 gene mutations in Spanish patients with primary open-angle glaucoma. *Mol. Vis.* 12:748–55
29. Melki R, Lefort N, Brezin AP, 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.* 11:1012–17
30. Stoilov I, Akarsu AN, 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.* 6:641–47
31. Akarsu AN, Turacli ME, Aktan SG, Barsoum-Homsy M, Chevrette L, et al. 1996. A second locus (GLC3B) for primary congenital glaucoma (Buphthalmos) maps to the 1p36 region. *Hum. Mol. Genet.* 5:1199–203
32. Stoilov IR, Sarfarazi M. 2002. The third genetic locus (GLC3C) for primary congenital glaucoma (PCG) maps to chromosome 14q24.3 *Invest. Ophthalmol. Vis. Sci.* 43:3015 (Abstr.)

33. Bejjani BA, Stockton DW, Lewis RA, Tomey KF, Dueker DK, et al. 2000. Multiple CYP1B1 mutations and incomplete penetrance in an inbred population segregating primary congenital glaucoma suggest frequent de novo events and a dominant modifier locus. *Hum. Mol. Genet.* 9:367–74
34. Francois J. 1980. Congenital glaucoma and its inheritance. *Ophthalmologica* 181:61–73
35. Gencik A, Gencikova A, Ferak V. 1982. Population genetical aspects of primary congenital glaucoma. I. Incidence, prevalence, gene frequency, and age of onset. *Hum. Genet.* 61:193–97
36. Nelson DR, Zeldin DC, Hoffman SM, Maltais LJ, Wain HM, Nebert DW. 2004. Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. *Pharmacogenetics* 14:1–18
37. Muskhelishvili L, Thompson PA, Kusewitt DF, Wang C, Kadlubar FF. 2001. In situ hybridization and immunohistochemical analysis of cytochrome P450 1B1 expression in human normal tissues. *J. Histochem. Cytochem.* 49:229–36
38. Sarfarazi M. 1997. Recent advances in molecular genetics of glaucomas. *Hum. Mol. Genet.* 6:1667–77
39. Vincent A, Billingsley G, Priston M, Williams-Lyn D, Sutherland J, et al. 2001. Phenotypic heterogeneity of CYP1B1: mutations in a patient with Peters' anomaly. *J. Med. Genet.* 38:324–26
40. Vincent A, Billingsley G, Priston M, Glaser T, Oliver E, et al. 2006. Further support of the role of CYP1B1 in patients with Peters anomaly. *Mol. Vis.* 12:506–10
41. Sitorus R, Ardjo SM, Lorenz B, Preising M. 2003. CYP1B1 gene analysis in primary congenital glaucoma in Indonesian and European patients. *J. Med. Genet.* 40:9e
42. Chavarria-Soley G, Michels-Rautenstrauss K, Caliebe A, Kautza M, Mardin C, Rautenstrauss B. 2006. Novel CYP1B1 and known PAX6 mutations in anterior segment dysgenesis (ASD). *J. Glaucoma* 15:499–504
43. Chavarria-Soley G, Michels-Rautenstrauss K, Pasutto F, Flikier D, Flikier P, et al. 2006. Primary congenital glaucoma and Rieger's anomaly: extended haplotypes reveal founder effects for eight distinct CYP1B1 mutations. *Mol. Vis.* 12:523–31
44. Panicker SG, Reddy AB, Mandal AK, Ahmed N, Nagarajaram HA, et al. 2002. Identification of novel mutations causing familial primary congenital glaucoma in Indian pedigrees. *Invest. Ophthalmol. Vis. Sci.* 43:1358–66
45. Soley GC, Bosse KA, Flikier D, Flikier P, Azofeifa J, et al. 2003. Primary congenital glaucoma: a novel single-nucleotide deletion and varying phenotypic expression for the 1546-1555dup mutation in the GLC3A (CYP1B1) gene in 2 families of different ethnic origin. *J. Glaucoma* 12:27–30
46. Lewis DFV, Gillam EMJ, Everett SA, Shimada T. 2003. Molecular modelling of human CYP1B1 substrate interactions and investigation of allelic variant effects on metabolism. *Chem. Biol. Interact.* 145:281–95

47. Achary MS, Reddy AB, Chakrabarti S, Panicker SG, Mandal AK, et al. 2006. Disease-causing mutations in proteins: structural analysis of the CYP1b1 mutations causing primary congenital glaucoma in humans. *Biophys. J.* 91:4329–39
48. Stoilov I, Akarsu AN, Alozie I, Child A, Barsoum-Homsy M, et al. 1998. Sequence analysis and homology modeling suggest that primary congenital glaucoma on 2p21 results from mutations disrupting either the hinge region or the conserved core structures of cytochrome P4501B1. *Am. J. Hum. Genet.* 62:573–84
49. Mashima Y, Suzuki Y, Sergeev Y, Ohtake Y, Tanino T, et al. 2001. Novel cytochrome P4501B1 (CYP1B1) gene mutations in Japanese patients with primary congenital glaucoma. *Invest. Ophthalmol. Vis. Sci.* 42:2211–16
50. Doshi M, Marcus C, Bejjani BA, Edward DP. 2006. Immunolocalization of CYP1B1 in normal, human, fetal and adult eyes. *Exp. Eye Res.* 82:24–32
51. Wirtz MK, Samples JR, Xu H, Severson T, Acott TS. 2002. Expression profile and genome location of cDNA clones from an infant human trabecular meshwork cell library. *Invest. Ophthalmol. Vis. Sci.* 43:3698–704
52. Tomarev SI, Wistow G, Raymond V, Dubois S, Malyukova I. 2003. Gene expression profile of the human trabecular meshwork: NEIBank sequence tag analysis. *Invest. Ophthalmol. Vis. Sci.* 44:2588–96
53. Choudhary D, Jansson I, Sarfarazi M, Schenkman JB. 2006. Physiological significance and expression of P450s in the developing eye. *Drug Metab. Rev.* 38:337–52
54. Bejjani BA, Xu L, Armstrong D, Lupski JR, Reneker LW. 2002. Expression patterns of cytochrome P4501B1 (Cyp1b1) in FVB/N mouse eyes. *Exp. Eye Res.* 75:249–57
55. Chambers D, Wilson L, Maden M, Lumsden A. 2007. RALDH-independent generation of retinoic acid during vertebrate embryogenesis by CYP1B1. *Development* 134:1369–83
56. Civan MM, Macknight AD. 2004. The ins and outs of aqueous humour secretion. *Exp. Eye Res.* 78:625–31
57. Buters JT, Sakai S, Richter T, Pineau T, Alexander DL, et al. 1999. Cytochrome P450 CYP1B1 determines susceptibility to 7,12-dimethylbenz[a]anthracene-induced lymphomas. *Proc. Natl. Acad. Sci. USA* 96:1977–82
58. Libby RT, Smith RS, Savinova OV, Zabaleta A, Martin JE, et al. 2003. Modification of ocular defects in mouse developmental glaucoma models by tyrosinase. *Science* 299:1578–81
59. van Dorp DB, Delleman JW, Loewer-Sieger DH. 1984. Oculocutaneous albinism and anterior chambre cleavage malformations. Not a coincidence. *Clin. Genet.* 26:440–44
60. Bidinost C, Hernandez N, Edward DP, Al-Rajhi A, Lewis RA, et al. 2006. Of mice and men: tyrosinase modification of congenital glaucoma in mice but not in humans. *Invest. Ophthalmol. Vis. Sci.* 47:1486–90
61. Tang YM, Wo YY, Stewart J, Hawkins AL, Griffin CA, et al. 1996. Isolation and characterization of the human cytochrome P450 CYP1B1 gene. *J. Biol. Chem.* 271:28324–30

62. Thier R, Bruning T, Roos PH, Bolt HM. 2002. Cytochrome P450 1B1, a new keystone in gene-environment interactions related to human head and neck cancer? *Arch. Toxicol.* 76:249–56
63. Hulsman CAA, Westendorp ICD, Ramrattan RS, Wolfs RCW, Witteman JCM, et al. 2001. Is open-angle glaucoma associated with early menopause? The Rotterdam Study. *Am. J. Epidemiol.* 154:138–44
64. Polansky JR, Fauss DJ, Chen P, Chen H, Lutjen-Drecoll E, et al. 1997. Cellular pharmacology and molecular biology of the trabecular meshwork inducible glucocorticoid response gene product. *Ophthalmologica* 211:126–39
65. Craig JE, Baird PN, Healey DL, McNaught AI, McCartney PJ, et al. 2001. Evidence for genetic heterogeneity within eight glaucoma families, with the GLC1A Gln368STOP mutation being an important phenotypic modifier. *Ophthalmology* 108:1607–20
66. Jansson I, Stoilov I, Sarfarazi M, Schenkman JB. 2001. Effect of two mutations of human CYP1B1, G61E and R469W, on stability and endogenous steroid substrate metabolism. *Pharmacogenetics* 11:793–801
67. Tsuchiya Y, Nakajima M, Yokoi T. 2005. Cytochrome P450-mediated metabolism of estrogens and its regulation in human. *Cancer Lett.* 227:115–24
68. Karypidis AH, Soderstrom T, Nordmark A, Granath F, Cnattingius S, Rane A. 2006. Association of cytochrome P450 1B1 polymorphism with first-trimester miscarriage. *Fertil. Steril.* 86:1498–503
69. Li DN, Seidel A, Pritchard MP, Wolf CR, Friedberg T. 2000. Polymorphisms in P450 CYP1B1 affect the conversion of estradiol to the potentially carcinogenic metabolite 4-hydroxyestradiol. *Pharmacogenetics* 10:343–53
70. Shimada T, Watanabe J, Kawajiri K, Sutter TR, Guengerich FP, et al. 1999. Catalytic properties of polymorphic human cytochrome P450 1B1 variants. *Carcinogenesis* 20:1607–13
71. Zheng W, Xie DW, Jin F, Cheng JR, Dai Q, et al. 2000. Genetic polymorphism of cytochrome P450-1B1 and risk of breast cancer. *Cancer Epidemiol. Biomarkers Prev.* 9:147–50
72. Bailey LR, Roodi N, Dupont WD, Parl FF. 1998. Association of cytochrome P450 1B1 (CYP1B1) polymorphism with steroid receptor status in breast cancer. *Cancer Res.* 58:5038–41
73. Capdevila JH, Falck JR. 2001. The CYP P450 arachidonic acid monooxygenases: from cell signaling to blood pressure regulation. *Biochem. Biophys. Res. Commun.* 285:571–76
74. Choudhary D, Jansson I, Stoilov I, Sarfarazi M, Schenkman JB. 2004. Metabolism of retinoids and arachidonic acid by human and mouse cytochrome P450 1b1. *Drug Metab. Dispos.* 32:840–47
75. Fitzpatrick FA, Murphy RC. 1988. Cytochrome P-450 metabolism of arachidonic acid: formation and biological actions of "epoxygenase"-derived eicosanoids. *Pharmacol. Rev.* 40:229–41
76. Masferrer JL, Rios AP, Schwartzman ML. 1990. Inhibition of renal, cardiac and corneal ($Na^{(+)}$-K^{+})ATPase by 12(R)-hydroxyeicosatetraenoic acid. *Biochem. Pharmacol.* 39:1971–74

77. Stiemke MM, Edelhauser HF, Geroski DH. 1991. The developing corneal endothelium: correlation of morphology, hydration and Na/K ATPase pump site density. *Curr. Eye Res.* 10:145–56
78. Masferrer JL, Dunn MW, Schwartzman ML. 1990. 12(R)-hydroxyeicosatetraenoic acid, an endogenous corneal arachidonate metabolite, lowers intraocular pressure in rabbits. *Invest. Ophthalmol. Vis. Sci.* 31:535–39
79. Duester G. 2000. Families of retinoid dehydrogenases regulating vitamin A function: production of visual pigment and retinoic acid. *Eur. J. Biochem.* 267:4315–24
80. Duester G, Mic FA, Molotkov A. 2003. Cytosolic retinoid dehydrogenases govern ubiquitous metabolism of retinol to retinaldehyde followed by tissue-specific metabolism to retinoic acid. *Chem. Biol. Interact.* 143–144:201–10
81. Clagett-Dame M, DeLuca HF. 2002. The role of vitamin A in mammalian reproduction and embryonic development. *Annu. Rev. Nutr.* 22:347–81
82. Dickman ED, Thaller C, Smith SM. 1997. Temporally-regulated retinoic acid depletion produces specific neural crest, ocular and nervous system defects. *Development* 124:3111–21
83. Collins MD, Mao GE. 1999. Teratology of retinoids. *Annu. Rev. Pharmacol. Toxicol.* 39:399–430
84. Fernandez-Salguero P, Pineau T, Hilbert DM, McPhail T, Lee SS, et al. 1995. Immune system impairment and hepatic fibrosis in mice lacking the dioxin-binding Ah receptor. *Science* 268:722–26
85. Andreola F, Fernandez-Salguero PM, Chiantore MV, Petkovich MP, Gonzalez FJ, De Luca LM. 1997. Aryl hydrocarbon receptor knockout mice ($AHR^{-/-}$) exhibit liver retinoid accumulation and reduced retinoic acid metabolism. *Cancer Res.* 57:2835–38
86. Andreola F, Calvisi DF, Elizondo G, Jakowlew SB, Mariano J, et al. 2004. Reversal of liver fibrosis in aryl hydrocarbon receptor null mice by dietary vitamin A depletion. *Hepatology* 39:157–66
87. Niederreither K, Abu-Abed S, Schuhbaur B, Petkovich M, Chambon P, Dolle P. 2002. Genetic evidence that oxidative derivatives of retinoic acid are not involved in retinoid signaling during mouse development. *Nat. Genet.* 31:84–88
88. Reijntjes S, Blentic A, Gale E, Maden M. 2005. The control of morphogen signalling: regulation of the synthesis and catabolism of retinoic acid in the developing embryo. *Dev. Biol.* 285:224–37
89. Pandi-Perumal SR, Srinivasan V, Maestroni GJ, Cardinali DP, Poeggeler B, Hardeland R. 2006. Melatonin: Nature's most versatile biological signal? *FEBS J.* 273:2813–38
90. Hardeland R, Pandi-Perumal SR, Cardinali DP. 2006. Melatonin. *Int. J. Biochem. Cell Biol.* 38:313–16
91. Tosini G, Menaker M. 1998. The clock in the mouse retina: melatonin synthesis and photoreceptor degeneration. *Brain Res.* 789:221–28
92. Mhatre MC, van Jaarsveld AS, Reiter RJ. 1988. Melatonin in the lacrimal gland: first demonstration and experimental manipulation. *Biochem. Biophys. Res. Commun.* 153:1186–92

93. Abe M, Itoh MT, Miyata M, Ishikawa S, Sumi Y. 1999. Detection of melatonin, its precursors and related enzyme activities in rabbit lens. *Exp. Eye Res.* 68:255–62
94. Abe M, Itoh MT, Miyata M, Shimizu K, Sumi Y. 2000. Circadian rhythm of serotonin N-acetyltransferase activity in rat lens. *Exp. Eye Res.* 70:805–8
95. Martin XD, Malina HZ, Brennan MC, Hendrickson PH, Lichter PR. 1992. The ciliary body—the third organ found to synthesize indoleamines in humans. *Eur. J. Ophthalmol.* 2:67–72
96. Cahill GM, Besharse JC. 1989. Retinal melatonin is metabolized within the eye of xenopus laevis. *Proc. Natl. Acad. Sci. USA* 86:1098–102
97. Chiou GC, Aimoto T, Chiou LY. 1985. Melatonergic involvement in diurnal changes of intraocular pressure in rabbit eyes. *Ophthalmic Res.* 17:373–78
98. Rohde BH, McLaughlin MA, Chiou LY. 1985. Existence and role of endogenous ocular melatonin. *J. Ocul. Pharmacol.* 1:235–43
99. Yu HS, Yee RW, Howes KA, Reiter RJ. 1990. Diurnal rhythms of immunoreactive melatonin in the aqueous humor and serum of male pigmented rabbits. *Neurosci. Lett.* 116:309–14
100. Liu JH, Dacus AC. 1991. Endogenous hormonal changes and circadian elevation of intraocular pressure. *Invest. Ophthalmol. Vis. Sci.* 32:496–500
101. Axelrod J. 1974. The pineal gland: a neurochemical transducer. *Science* 184:1341–48
102. Iuvone PM, Bernard M, Alonso-Gomez A, Greve P, Cassone VM, Klein DC. 1997. Cellular and molecular regulation of serotonin N-acetyltransferase activity in chicken retinal photoreceptors. *Biol. Signals* 6:217–24
103. Boutin JA, Audinot V, Ferry G, Delagrange P. 2005. Molecular tools to study melatonin pathways and actions. *Trends Pharmacol. Sci.* 26:412–19
104. Young IM, Leone RM, Francis P, Stovell P, Silman RE. 1985. Melatonin is metabolized to N-acetyl serotonin and 6-hydroxymelatonin in man. *J. Clin. Endocrinol. Metab.* 60:114–19
105. Ma X, Idle JR, Krausz KW, Gonzalez FJ. 2005. Metabolism of melatonin by human cytochromes p450. *Drug Metab. Dispos.* 33:489–94
106. Hirata F, Hayaishi O, Tokuyama T, Seno S. 1974. In vitro and in vivo formation of two new metabolites of melatonin. *J. Biol. Chem.* 249:1311–13
107. Allegra M, Furtmuller PG, Regelsberger G, Turco-Liveri ML, Tesoriere L, et al. 2001. Mechanism of reaction of melatonin with human myeloperoxidase. *Biochem. Biophys. Res. Commun.* 282:380–86
108. Ma X, Idle JR, Krausz KW, Tan DX, Ceraulo L, Gonzalez FJ. 2006. Urinary metabolites and antioxidant products of exogenous melatonin in the mouse. *J. Pineal Res.* 40:343–49
109. Pierce ME, Besharse JC. 1985. Circadian regulation of retinomotor movements. I. Interaction of melatonin and dopamine in the control of cone length. *J. Gen. Physiol.* 86:671–89
110. Dubocovich ML. 1983. Melatonin is a potent modulator of dopamine release in the retina. *Nature* 306:782–84
111. Doyle SE, Grace MS, McIvor W, Menaker M. 2002. Circadian rhythms of dopamine in mouse retina: the role of melatonin. *Vis. Neurosci.* 19:593–601

112. Besharse JC, Dunis DA. 1983. Methoxyindoles and photoreceptor metabolism: activation of rod shedding. *Science* 219:1341–43
113. Rada JA, Wiechmann AF. 2006. Melatonin receptors in chick ocular tissues: implications for a role of melatonin in ocular growth regulation. *Invest. Ophthalmol. Vis. Sci.* 47:25–33
114. Lundmark PO, Pandi-Perumal SR, Srinivasan V, Cardinali DP, Rosenstein RE. 2007. Melatonin in the eye: implications for glaucoma. *Exp. Eye Res.* 84:1021–30
115. Osborne NN, Chidlow G. 1994. The presence of functional melatonin receptors in the iris-ciliary processes of the rabbit eye. *Exp. Eye Res.* 59:3–9
116. Wiechmann AF, Wirsig-Wiechmann CR. 2001. Melatonin receptor mRNA and protein expression in *Xenopus laevis* nonpigmented ciliary epithelial cells. *Exp. Eye Res.* 73:617–23
117. Osborne NN. 1994. Serotonin and melatonin in the iris/ciliary processes and their involvement in intraocular pressure. *Acta Neurobiol. Exp.* 54(Suppl.):57–64
118. Pintor J, Martin L, Pelaez T, Hoyle CHV, Peral A. 2001. Involvement of melatonin MT3 receptors in the regulation of intraocular pressure in rabbits. *Eur. J. Pharmacol.* 416:251–54
119. Pintor J, Pelaez T, Hoyle CHV, Peral A. 2002. Ocular hypotensive effects of melatonin receptor agonists in the rabbit: further evidence for an MT3 receptor. *Br. J. Pharmacol.* 138:831–36
120. Serle JB, Wang RF, Peterson WM, Plourde R, Yerxa BR. 2004. Effect of 5-MCA-NAT, a putative melatonin MT3 receptor agonist, on intraocular pressure in glaucomatous monkey eyes. *J. Glaucoma.* 13:385–88
121. Rohde BH, Li BH, Chiou GC. 1993. Effects of melatonin and haloperidol given via vortex vein on the intraocular pressure. *Ophthal. Res.* 25:10–15
122. Samples JR, Krause G, Lewy AJ. 1988. Effect of melatonin on intraocular pressure. *Curr. Eye Res.* 7:649–53
123. Sissung TM, Price DK, Sparreboom A, Figg WD. 2006. Pharmacogenetics and regulation of human cytochrome P450 1B1: implications in hormone-mediated tumor metabolism and a novel target for therapeutic intervention. *Mol. Cancer Res.* 4:135–50
124. Sheffield VC, Stone EM, Alward WLM, Drack AV, Johnson AT, et al. 1993. Genetic linkage of familial open angle glaucoma to chromosome 1q21-q31. *Nat. Genet.* 4:47–50
125. Stoilova D, Child A, Trifan OC, Crick RP, Coakes RL, Sarfarazi M. 1996. Localization of a locus (GLC1B) for adult-onset primary open angle glaucoma to the 2cen-q13 region. *Genomics* 36:142–50
126. Wirtz MK, Samples JR, Kramer PL, Rust K, Topinka JR, et al. 1997. Mapping a gene for adult-onset primary open-angle glaucoma to chromosome 3q. *Am. J. Hum. Genet.* 60:296–304
127. Trifan OC, Traboulsi EI, Stoilova D, Alozie I, Nguyen R, et al. 1998. A third locus (GLC1D) for adult-onset primary open-angle glaucoma maps to the 8q23 region. *Am. J. Ophthalmol.* 126:17–28
128. Wirtz MK, Samples JR, Rust K, Lie J, Nordling L, et al. 1999. GLC1F, a new primary open-angle glaucoma locus, maps to 7q35-q36. *Arch. Ophthalmol.* 117:237–41

129. Suriyapperuma SP, Child A, Desai T, Brice G, Kerr A, et al. 2007. A new locus (GLC1H) for adult-onset primary open-angle glaucoma maps to the 2p15-p16 region. *Arch. Ophthalmol.* 125:86–92
130. Allingham RR, Wiggs JL, Hauser ER, Larocque-Abramson KR, Santiago-Turla C, et al. 2005. Early adult-onset POAG linked to 15q11–13 using ordered subset analysis. *Invest. Ophthalmol. Vis. Sci.* 46:2002–5
131. Wiggs JL, Lynch S, Ynagi G, Maselli M, Auguste J, et al. 2004. A genomewide scan identifies novel early-onset primary open-angle glaucoma loci on 9q22 and 20p12. *Am. J. Hum. Genet.* 74:1314–20
132. Kakiuchi-Matsumoto T, Isashiki Y, Ohba N, Kimura K, Sonoda S, Unoki K. 2001. Cytochrome P450 1B1 gene mutations in Japanese patients with primary congenital glaucoma. *Am. J. Ophthalmol.* 131:345–50
133. Bejjani BA, Lewis RA, Tomey KF, Anderson KL, Dueker DK, et al. 1998. Mutations in CYP1B1, the gene for cytochrome P4501B1, are the predominant cause of primary congenital glaucoma in Saudi Arabia. *Am. J. Hum. Genet.* 62:325–33
134. Alfadhli S, Behbehani A, Elshafey A, Abdelmoaty S, Al-Awadi S. 2006. Molecular and clinical evaluation of primary congenital glaucoma in Kuwait. *Am. J. Ophthalmol.* 141:512–16
135. Hollander DA, Sarfarazi M, Stoilov I, Wood IS, Fredrick DR, Alvarado JA. 2006. Genotype and phenotype correlations in congenital glaucoma: CYP1B1 mutations, goniodysgenesis, and clinical characteristics. *Am. J. Ophthalmol.* 142:993–1004
136. Michels-Rautenstrauss KG, Mardin CY, Zenker M, Jordan N, Gusek-Schneider GC, Rautenstrauss BW. 2001. Primary congenital glaucoma: three case reports on novel mutations and combinations of mutations in the GLC3A (CYP1B1) gene. *J. Glaucoma.* 10:354–57
137. Colomb E, Kaplan J, Garchon HJ. 2003. Novel cytochrome P450 1B1 (CYP1B1) mutations in patients with primary congenital glaucoma in France. *Hum. Mutat.* 22:496
138. Ohtake Y, Kubota R, Tanino T, Miyata H, Mashima Y. 2000. Novel compound heterozygous mutations in the cytochrome P4501B1 gene (CYP1B1) in a Japanese patient with primary congenital glaucoma. *Ophthalmic Genet.* 21:191–93
139. Stoilov IR, Costa VP, Vasconcellos JP, Melo MB, Betinjane AJ, et al. 2002. Molecular genetics of primary congenital glaucoma in Brazil. *Invest. Ophthalmol. Vis. Sci.* 43:1820–27
140. Plasilova M, Stoilov I, Sarfarazi M, Kadasi L, Ferakova E, Ferak V. 1999. Identification of a single ancestral CYP1B1 mutation in Slovak Gypsies (Roms) affected with primary congenital glaucoma. *J. Med. Genet.* 36:290–94
141. Curry SM, Daou AG, Hermanns P, Molinari A, Lewis RA, Bejjani BA. 2004. Cytochrome P4501B1 mutations cause only part of primary congenital glaucoma in Ecuador. *Ophthal. Genet.* 25:3–9
142. Reddy AB, Panicker SG, Mandal AK, Hasnain SE, Balasubramanian D. 2003. Identification of R368H as a predominant CYP1B1 allele causing primary congenital glaucoma in Indian patients. *Invest. Ophthalmol. Vis. Sci.* 44:4200–3

143. Belmouden A, Melki R, Hamdani M, Zaghloul K, Amraoui A, et al. 2002. A novel frameshift founder mutation in the cytochrome P450 1B1 (CYP1B1) gene is associated with primary congenital glaucoma in Morocco. *Clin. Genet.* 62:334–39
144. Messina-Baas OM, Gonzalez-Huerta LM, Chima-Galan C, Kofman-Alfaro SH, Rivera-Vega MR, et al. 2006. Molecular analysis of the CYP1B1 gene: identification of novel truncating mutations in patients with primary congenital glaucoma. *Ophthal. Res.* 39:17–23
145. Sena DF, Finzi S, Rodgers K, Del BE, Haines JL, Wiggs JL. 2004. Founder mutations of CYP1B1 gene in patients with congenital glaucoma from the United States and Brazil. *J. Med. Genet.* 41:e6
146. Baird PN, Foote SJ, Mackey DA, Craig J, Speed TP, Bureau A. 2005. Evidence for a novel glaucoma locus at chromosome 3p21-22. *Hum. Genet.* 117:249–57
147. Pang CP, Fan BJ, Canlas O, Wang DY, Dubois S, et al. 2006. A genome-wide scan maps a novel juvenile-onset primary open angle glaucoma locus to chromosome 5q. *Mol. Vis.* 12:85–92
148. Wang DY, Fan BJ, Chua JK, Tam PO, Leung CK, et al. 2006. A genome-wide scan maps a novel juvenile-onset primary open-angle glaucoma locus to 15q. *Invest. Ophthalmol. Vis. Sci.* 47:5315–21
149. Hollander DA, Sarfarazi M, Stoilov I, Wood IS, Fredrick DR, Alvarado JA. 2006. Genotype and phenotype correlations in congenital glaucoma: CYP1B1 mutations, goniodysgenesis, and clinical characteristics. *Am. J. Ophthalmol.* 142:993–1004
150. Strom CM, Strom S, Redman Ms J, Sun W. 2006. Prenatal diagnosis for primary congenital glaucoma (bupthalmous). *Prenat. Diagn.* 26:877
151. Hollander DA, Sarfarazi M, Stoilov I, Wood IS, Fredrick DR, Alvarado JA. 2006. Genotype and phenotype correlations in congenital glaucoma. *Trans. Am. Ophthalmol. Soc.* 104:183–95

Annual Review of Pharmacology and Toxicology

Volume 48, 2008

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Pharmacology and Toxicology* articles may be found at http://pharmtox.annualreviews.org/errata.shtml