Of Mice and Men: Tyrosinase Modification of Congenital Glaucoma in Mice but Not in Humans

Carla Bidinost,[1] *Natalie Hernandez,*[1,2] *Deepak P. Edward,*[3] *Ali Al-Rajhi,*[4] *Richard Alan Lewis,*[4,5,6,7,8] *James R. Lupski,*[5,7] *David W. Stockton,*[5,6,8] *and Bassem A. Bejjani*[1,2]

Purpose. Primary congenital glaucoma (PCG) is an autosomal recessive ocular trait caused by mutations in the gene for cytochrome P4501B1 (*CYP1B1*). Although PCG is often considered to be fully penetrant, the disease shows 50% penetrance in some Saudi Arabian families. The familial segregation of the nonpenetrance suggests a genetic modifier. Recently, tyrosinase (*Tyr*) deficiency was found to worsen the drainage structure/ocular dysgenesis phenotype of *Cyp1b1*$^{-/-}$ mice, suggesting that *Tyr* is a modifier of the phenotype. In the current study, tyrosinase (*TYR*) was investigated in human PCG.

Methods. A genome-wide screen, a single nucleotide polymorphism (SNP) analysis in the *TYR* chromosomal region 11q13-q21, and sequencing of the *TYR* gene was performed with individuals from Saudi Arabian families with multiple, clinically confirmed, molecularly proven, nonpenetrant members.

Results. The study outcome did not support *TYR* as a modifier of the PCG phenotype in this population. The sequencing data showed no *TYR* mutations in the nonpenetrant family members and no difference in polymorphism frequencies between nonpenetrant or fully penetrant families.

Conclusions. *TYR* is not a modifier of the *CYP1B1*-associated PCG phenotype in the Saudi Arabian population. (*Invest Ophthalmol Vis Sci.* 2006;47:1486–1490) DOI:10.1167/iovs.05-0763

In previous work, we showed that 94% of individuals with primary congenital glaucoma (PCG) in Saudi Arabia have homozygous or compound heterozygous mutations in *CYP1B1* and that 29% of families with PCG in this population show 50% penetrance.[1–3] In these families, half of the study subjects with molecularly proven homozygous or compound heterozygous *CYP1B1* mutations show no evidence of glaucoma in childhood. Some individuals also have a normal ocular examination even in adolescence and adulthood. Two of us (BAB, DPE) recently confirmed the normal phenotype in many asymptomatic and clinically normal individuals ($n = 8$; ages, 7–28 years old) who have identical homozygous *CYP1B1* mutations (G61E) to their unequivocally affected siblings (Table 1). Less than complete penetrance of PCG has not been reported in any other population.[4–13] Several possible explanations have been espoused for the reduced penetrance in this population. Perhaps the large sizes of sibships or families in Saudi Arabia contributed to the recognition of the segregation distortion, and it was merely overlooked in populations with small nuclear families. Alternatively, a potential environmental factor in Saudi Arabia protects individuals at genetic risk. Or perhaps other genetic loci decrease the susceptibility to the clinical disorder. It is unlikely that the observation has been missed in other populations because of small family sizes, since some large families studied have no nonpenetrant individuals (Bejjani BA, unpublished data, 2005). Similarly, in reports of populations geographically close to Saudi Arabia and in fact in some families in our sample from Saudi Arabia, penetrance is not reduced. These observations do not prove that there is no environmental modifier; however, it seems to make it less likely. The working hypothesis for reduced penetrance in the Saudi population invokes an independently segregating genetic locus that decreases the susceptibility to development of clinical disease. Genetic data suggest that a modifier of the PCG phenotype in this population may behave as a dominant allele.[3]

Recently, the tyrosinase gene (*Tyr*) was shown to modify the phenotype of *Cyp1b1*$^{-/-}$ mice.[14] Tyrosinase deficiency exacerbated the change in angle structure–ocular dysgenesis phenotype in these mice.[14] In addition, the ocular dysgenesis in *Cyp1b1*$^{-/-}$, *Tyr*$^{-/-}$ mice was alleviated by the administration of oral dihydroxyphenylalanine (L-dopa) to the pregnant mothers. L-Dopa is the product of tyrosinase mono-oxygenation of tyrosine, thereby bypassing the need for Tyr. These experiments suggest that a pathway involving tyrosinase and L-dopa (or an L-dopa metabolite) participates in either the formation or the function of the anterior chamber drainage structures or functions during prenatal development. Based on these findings, we hypothesized that variation of tyrosinase in humans may modify the PCG phenotype. If this were the case, then genes or drugs affecting L-dopa levels would modify the deleterious effects of *CYP1B1* mutations. Such a possibility would provide an opportunity to investigate possible therapies to reduce the incidence or severity of glaucoma in at-risk families. In the current study, we evaluated the possible role of tyrosinase (*TYR*) in the modification of the human PCG phenotype by linkage, single nucleotide polymorphism (SNP) analysis, and sequencing. Our data do not support *TYR* as a major modifier of the PCG phenotype in the Saudi population.

Methods

Each subject, or the responsible adult on behalf of minors, signed a consent for participation in these investigations that was approved by

From the [1]Health Research and Education Center, Washington State University Spokane, Spokane, Washington; the [2]Sacred Heart Medical Center, Spokane, Washington; the [3]Department of Ophthalmology, University of Illinois in Chicago, Chicago, Illinois; the [4]King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia; and the Departments of [5]Molecular and Human Genetics, [6]Medicine, [7]Pediatrics, and [8]Ophthalmology, Baylor College of Medicine, Houston, Texas.

Supported by National Eye Institute Grant R01 EY11780 (BAB). RAL is a Senior Scientific Investigator of Research to Prevent Blindness.

Submitted for publication June 16, 2005; revised November 8, 2005; accepted February 9, 2006.

Disclosure: **C. Bidinost**, None; **N. Hernandez**, None; **D.P. Edward**, None; **A. Al-Rajhi**, None; **R.A. Lewis**, None; **J.R. Lupski**, None; **D.W. Stockton**, None; **B.A. Bejjani**, None;

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Bassem A. Bejjani, Health Research and Education Center, Washington State University Spokane, PO Box 1495, Spokane, WA 99210-1495, bejjani@wsu.edu.

Investigative Ophthalmology & Visual Science, April 2006, Vol. 47, No. 4

TABLE 1. Clinical Examination of Eight Nonpenetrant Individuals 10 Years after Initial Enrollment

Family	Individual	Age at 2nd Examination (y)	Genotype	Phenotype	Treatment
105	105–08	12	G61E/G61E	IOP: 14/14 mm Hg; K diameter: 12/12; cornea: clear	None
	105–22	7	G61E/G61E	IOP: 19/37 mm Hg; K diameter: 13/14; cornea: clear	None; referred to KKESH for further evaluation and therapy
113	113–09	19	G61E/G61E	IOP: 27/27 mm Hg; K diameter: 12/12; cornea: clear	None
	113–13	11	G61E/G61E	IOP: 27/13 mm Hg; K diameter: 12/12; cornea: clear	None
137	137–12	28	G61E/G61E	IOP: 14/14 mm Hg; K diameter: 11.5/11.5; cornea: clear	None
	137–13	27	G61E/G61E	IOP: 22/22 mm Hg; K diameter: 12/12; cornea: clear	None
143	143–05	17	G61E/G61E	IOP: 17.3/17.3 mm Hg; K diameter: 12/12; cornea: clear	None
	143–06	15	G61E/G61E	IOP: 14/14 mm Hg; K diameter: 12/12; cornea: clear	None

the appropriate Institutional Review Boards for Human Subject Research in the United States and Saudi Arabia. The study research adhered to tenets of the Declaration of Helsinki.

We performed a genome-wide screen of 97 individuals from 17 Saudi Arabian families with multiple nonpenetrant members. Fifty-eight of these 97 individuals were molecularly proven to have homozygous or compound heterozygous *CYP1B1* mutations. Thirty-three of the 58 were affected, and 25 were clinically confirmed to have normal corneal diameters, normal intraocular pressures, and normal-appearing optic nerves. Eight of these 25 nonpenetrant patients underwent two independent ophthalmic examinations separated by 10 years (Table 1). The additional 39 individuals were normal parents or siblings with one or no mutant *CYP1B1* alleles. Genotyping data were generated by linkage mapping (PRISM Linkage Mapping Set; Applied Biosystems, Inc., Foster City, CA). Data were evaluated with both nonparametric and parametric linkage techniques, with susceptibility or protection, and with both dominant and recessive models (data not shown).

SNP analysis spanning the *TYR* gene (Fig. 1) was realized in 96 individuals from 19 Saudi Arabian families with nonpenetrant members. These 96 individuals included 87 individuals from the same 17 families studied for the genome-wide screen plus 9 more individuals from two other nonpenetrant families. In both studies, the relative number of affected, nonpenetrant, and normal control individuals were 34%, 26%, and 40%, respectively. SNPs were chosen from the SNP database (http://www.ncbi.nlm.nih.gov/SNP/ provided in the public domain by the National Center for Biotechnology Information, Bethesda, MD); the assays were designed with assay design software (Sequenom, Inc., San Diego, CA). Data were recorded for affected, carrier, and control individuals.

The five exons of the *TYR* gene were sequenced. We selected for analysis 60 individuals with homozygous or compound heterozygous mutations in *CYP1B1* from the same 19 nonpenetrant families. Thirty-three of these individuals were nonpenetrant, and 27 had full expression of the disease. In addition, 50 individuals with PCG were selected at random from 24 Saudi Arabian families that had no nonpenetrant individuals. We also studied 50 unrelated and unaffected Saudi control subjects with no family history of hereditary eye disease and 50 unaffected white control subjects. The sequences of the *TYR* primers are shown in Table 2. All amplification reactions were performed with standard PCR conditions in a thermal cycler (GeneAmp PCR system 9700; Perkin Elmer, Wellesley, MA). The amplified products were purified (QIAquick PCR Purification Kit; Qiagen, Valencia, CA) and sequenced (BigDye Terminator Cycle Sequencing Ready Reaction DNA sequencing kit; ABI) in the forward and reverse directions, according to the manufacturer's recommendations. Sequencing results were recorded on a genetic analyzer (PRISM 3100; ABI), according to the manufacturer's recommendations. The data were analyzed (Sequencher ver. 3.1.1 software; Gene Codes, Ann Arbor, MI).

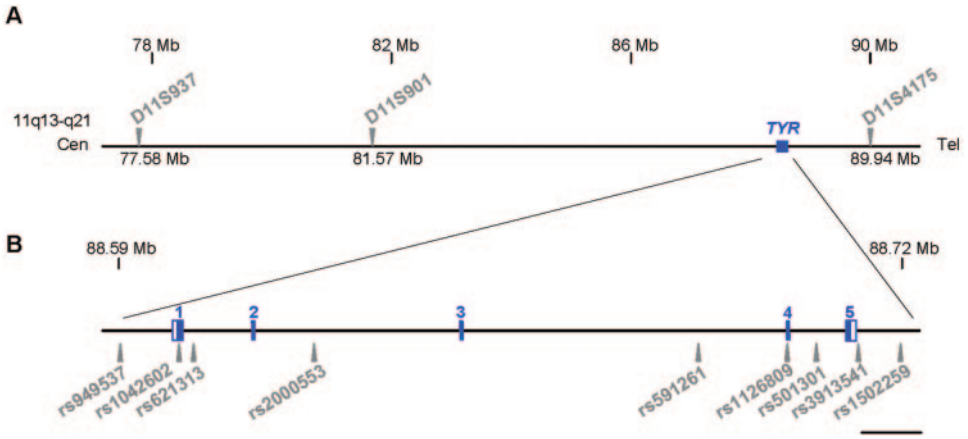

FIGURE 1. Genetic map of *TYR* locus on 11q13-q21. (**A**) Position of the genotyping markers used for linkage in 11q13-q21. Cen, centromeric side; Tel, telomeric side. (**B**) Position of the SNPs used for linkage in and around the *TYR* gene. *TYR* exons and the number of the exons are in *blue*. Bar, 10 kb.

TABLE 2. Primer Pair Sequences Used for PCR Amplification of *TYR* Exons

Exon	Primer Sequences
1 - F	5′ GGTCTCAGCCAAGACATGTGA 3′
1 - R	5′ ACAGGGCACCATTTCT 3′
2 - F	5′ AACATTTCTGCCTTCTCCTAC 3′
2 - R	5′ CACAGCCTCCCAAGTAAACTG 3′
3 - F	5′ AAGAGTCTCAATACGGAA 3′
3 - R	5′ CTTAAATCACATTTGATAGGC 3′
4 - F	5′ CCTTATTTTACTTTAAAAATT 3′
4 - R	5′ GGCCTATGTTAAGCAA 3′
5 - F	5′ CCCAAGCTCTTACAGT 3′
5 - R	5′ ATGGTCTTTACAGAAAAATAC 3′

TABLE 3. Lod Score for Markers around *TYR* on 11q13-q21

	Parametric Lod Score* (θ)							
Marker	**0.00**	**0.01**	**0.05**	**0.10**	**0.20**	**0.30**	**0.40**	**NPL† Score**
Dominant protective								
D11S937	−1.01	−0.93	−0.66	−0.45	−0.21	−0.08	−0.02	−0.79 (P = 1.00)
D11S901	−2.31	−1.87	−1.11	−0.69	−0.29	−0.11	−0.02	−0.50 (P = 0.74)
D11S4175	−1.40	−0.91	−0.38	−0.18	−0.05	−0.01	0.00	0.44 (P = 0.32)
Dominant liability								
D11S937	−0.19	−0.16	−0.07	−0.02	0.00	0.00	−0.01	0.00 (P = 1.00)
D11S901	−0.69	−0.61	−0.33	−0.11	0.07	0.08	0.03	−0.81 (P = 1.00)
D11S4175	−0.27	−0.25	−0.18	−0.12	−0.06	−0.03	−0.01	0.15 (P = 0.31)
Recessive protective								
D11S937	−0.63	−0.55	−0.33	−0.18	−0.05	−0.02	−0.01	
D11S901	−2.91	−2.48	−1.49	−0.90	−0.34	−0.11	−0.02	
D11S4175	−2.32	−1.65	−0.94	−0.60	−0.27	−0.11	−0.03	
Recessive liability								
D11S937	−0.99	−0.92	−0.68	−0.47	−0.20	−0.08	−0.02	
D11S901	−0.26	−0.25	−0.15	−0.03	0.06	0.06	0.02	
D11S4175	0.20	0.23	0.29	0.30	0.23	0.12	0.03	

* Recombination fractions.
† Nonparametric lod score.

TABLE 4. Frequency of Polymorphisms in *TYR* Gene Exons 1 and 4 in Different Populations

		Exon 1 575C→A (S192Y)			Exon 4 1205G→A (R402Q)		
Population	***n****	**C/C**	**C/A**	**A/A**	**G/G**	**G/A**	**A/A**
Nonpenetrant Families							
Total	60	48 (80.0)	12 (20.0)	0	54 (90.0)	6 (10.0)	0
Affected	27	21 (77.8)	6 (22.2)	0	24 (88.9)	3 (11.1)	0
Nonpenetrant	33	27 (81.8)	6 (18.2)	0	30 (90.9)	3 (9.1)	0
Fully penetrant families	50	41 (82.0)	9 (18.0)	0	38 (76.0)	10 (20.0)	2 (4.0)
Saudi control subjects	50	39 (78.0)	10 (20.0)	1 (2.0)	30 (60.0)	19 (38.0)	1 (2.0)
Non-Saudi control subjects	50	18 (36.0)	24 (48.0)	8 (16.0)	30 (60.0)	20 (40.0)	0

* Individuals tested.
The values indicate the number of individuals having each genotype (percentage).

TABLE 5. Independent Sample Frequency of Polymorphism in *TYR* Exon 4 in Study Subjects with Homozygous and Compound Heterozygous *CYP1B1* Mutations

	Exon 1 575C→A (S192Y)			Exon 4 1205G→A (R402Q)		
Population	**C/C**	**C/A**	**A/A**	**G/G**	**G/A**	**A/A**
Nonpenetrant	16.0	3.0	0.0	15.5	3.5	0.0
Fully penetrant	15.8	3.2	0.0	17.4	4.9	0.7

The values indicate the absolute counts as if one sample per pedigree had been randomly collected from each of the 19 nonpenetrant families or the 24 fully penetrant families.

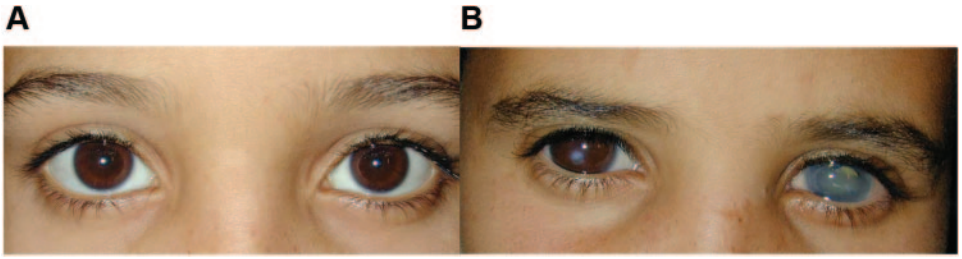

FIGURE 2. Siblings with identical homozygous *CYP1B1* mutations. (**A**) No evidence of disease; (**B**) severe bilateral disease. The more severely affected individual showed no differences in skin, hair, or ocular pigmentation.

RESULTS

A genome-wide screen with 97 individuals from 17 Saudi Arabian families with multiple, clinically confirmed, molecularly proven, nonpenetrant members did not identify any statistically significant evidence for a cosegregating locus, making the hypothesis of a single genetic modifier locus less appealing.

The genotype data from the genome screen previously completed were reanalyzed for the several markers that most closely flank the *TYR* locus on chromosome 11 at region q13-q21 (http://www.ensembl.org[15]), *D11S937*, *D11S901*, and *D11S4175* (Fig. 1A). A targeted two-point linkage analysis confirmed the previous linkage results that no lod score was significantly positive at any of these three markers (Table 3). The analysis of SNPs spanning the *TYR* gene (Fig. 1B) in 96 individuals from 19 nonpenetrant families showed no significant linkage to the *TYR* locus either (data not shown).

The sequencing of the *TYR* gene did not show any alteration in any of the 60 individuals with homozygous or compound heterozygous mutations in *CYP1B1* from 19 nonpenetrant families. We identified two coding polymorphisms, one in exon 1 (575C→A, S192Y) and another in exon 4 (1205G→A, R402Q) already described in the Mutation Database of the *TYR* Gene (http://www.retina-international.com/sci-news/tyrmut.htm/ provided in the public domain by Retina International's Scientific Newsletter and maintained by Markus Preising, Molecular Genetics Laboratory. University of Regensberg, Germany). Table 4 shows the observed genotype data for individuals from nonpenetrant families, fully penetrant families, Saudi control subjects, and non-Saudi control subjects. The exon 1 polymorphism showed a similar distribution of alleles in affected individuals, in their nonpenetrant relatives, in individuals from fully penetrant Saudi families, and in Saudi control subjects who do not have PCG (18.0%–22.2%; Table 4). This differed significantly from the non-Saudi control subjects, who had a higher frequency of the A allele ($P < 10^{-5}$). The exon 4 polymorphism also showed similar distribution of alleles between affected individuals and their nonpenetrant relatives (9.1%–11.1%), although the frequency of heterozygosity for the variant is slightly higher in the fully penetrant families than in the nonpenetrant (20.0%) ones. Also, this frequency is even higher in the Saudi control subjects, who do not have PCG and in non-Saudi control subjects (38.0%–40.0%; Table 4). Because multiple individuals are included from some families, these are not independent samples. To adjust for this, a weighted average was generated representing one individual randomly selected from each family. These data are shown in Table 5. The differences are not statistically significant ($\chi^2 = 6.49$; 3 *df*; $P = 0.371$). Our sequencing data do not support *TYR* as a major modifier of the PCG phenotype in the Saudi population.

DISCUSSION

The recent report of *Tyr* as a possible modifier for anterior segment dysgenesis in the *Cyp1b1*$^{-/-}$ mouse provided an attractive functional candidate for a genetic modifier of PCG in humans. The PCG cohort from Saudi Arabia is a unique population because of the high prevalence of *CYP1B1* mutations, probably as the result of both the high coefficient of inbreeding and large family sizes. These attributes offer an opportunity to test whether *TYR* is a modifier of the PCG phenotype in this population. Physical examination of many nonpenetrant individuals did not reveal any substantive difference in cutaneous or ocular pigmentation compared with their fully penetrant relatives (Fig. 2).

Studies of reduced penetrance in both recessive and maternally inherited deafness identified modifier genes by linkage analysis.[16,17] In contrast, however, we found no evidence for linkage (lod scores $< +2$) of *TYR* with the glaucoma phenotype or with the nonglaucoma phenotype within the families with incomplete penetrance. Nevertheless, it is still possible that *TYR* is a minor modifier in this population. *TRP1* and *TRP2* genes, which participate in L-dopa metabolism, are also candidates for the modification of the phenotype in PCG. The segregation of haplotypes for markers close to these genes (*D3S1263* for *TRP1* and *D13S1241* for *TRP2*) showed no correlation with the nonpenetrant phenotype (data not shown).

We identified nonpenetrant individuals in families with homozygous missense mutations (G61E), compound heterozygous mutations (G61E/R469W, G61E/D374N) and a homozygous nonsense mutation (4238del10). However, the majority of these (16 of the 19 nonpenetrant families), have the same homozygous *CYP1B1* mutation (G61E).[3] This mutation produces a change in a conserved amino acid but does not interrupt the synthesis of the protein as does the knockout in the mouse.[14] In fact, most of our study subjects carried recessive missense mutations in *CYP1B1,* some of which have been shown to have residual enzymatic activities.[18] Because the putative molecular mechanism of interaction between CYP1B1 and TYR is not known, a modifier effect of *TYR* on other *CYP1B1* human mutations cannot be excluded.

It is also possible that the role of TYR in normal human eye development is different from that in the murine mouse model due to intrinsic, yet unidentified differences between mice and humans.

The frequency of anterior segment dysgenesis and infantile glaucoma in patients with albinism,[19,20] the presence of an avian model of congenital glaucoma in the Albino Japanese quail (*Coturnix coturnix japonica*)[21,22] and the recent work on the mouse model[14] suggest that tyrosinase or related pigment-associated molecules play a role in trabecular meshwork or angle formation or function. The specific role(s) for these

molecules in formation of the iridocorneal angle and the nature of their interaction with CYP1B1 should be refined.

References

1. Anderson KL, Lewis RA, Bejjani BA, et al. A gene for primary congenital glaucoma is not linked to the locus on chromosome 1q for autosomal dominant juvenile-onset open angle glaucoma. *J Glaucoma*. 1996;5:416–421.
2. Bejjani BA, Lewis RA, Tomey KF, et al. Mutations in CYP1B1, the gene for cytochrome P4501B1, are the predominant cause of primary congenital glaucoma in Saudi Arabia. *Am J Hum Genet*. 1998;62:325–333.
3. Bejjani BA, Stockton DW, Lewis RA, et al. Multiple CYP1B1 mutations and incomplete penetrance in an inbred population segregating primary congenital glaucoma suggest frequent de novo events and a dominant modifier locus (published correction in *Hum Mol Genet*. 2000;9:1141) *Hum Mol Genet* 2000;9:367–374.
4. Gencik A, Gencikova A, Gerinec A. Genetic heterogeneity of congenital glaucoma. *Clin Genet*. 1980;17:241–248.
5. Akarsu AN, Turacli ME, Aktan SG, et al. A second locus (GLC3B) for primary congenital glaucoma (buphthalmos) maps to the 1p36 region. *Hum Mol Genet*. 1996;5:1199–1203.
6. Stoilov I, Akarsu AN, Alozie I, et al. 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*. 1998;62:573–584.
7. Plasilova M, Stoilov I, Sarfarazi M, Kadasi L, Ferakova E, Ferak V. Identification of a single ancestral CYP1B1 mutation in Slovak Gypsies (Roms) affected with primary congenital glaucoma. *J Med Genet*. 1999;36:290–294.
8. Panicker SG, Reddy AB, Mandal AK, et al. Identification of novel mutations causing familial primary congenital glaucoma in Indian pedigrees. *Invest Ophthalmol Vis Sci*. 2002;43:1358–1366.
9. Stoilov IR, Costa VP, Vasconcellos JP, et al. Molecular genetics of primary congenital glaucoma in Brazil. *Invest Ophthalmol Vis Sci*. 2002;43:1820–1827.
10. Colomb E, Kaplan J, Garchon HJ. Novel cytochrome P450 1B1 (CYP1B1) mutations in patients with primary congenital glaucoma in France. *Hum Mutat*. 2003;22:496.
11. Reddy AB, Panicker SG, Mandal AK, Hasnain SE, Balasubramanian D. Identification of R368H as a predominant CYP1B1 allele causing primary congenital glaucoma in Indian patients. *Invest Ophthalmol Vis Sci*. 2003;44:4200–4203.
12. Curry SM, Daou AG, Hermanns P, Molinari A, Lewis RA, Bejjani BA. Cytochrome P4501B1 mutations cause only part of primary congenital glaucoma in Ecuador. *Ophthalmic Genet*. 2004;25:3–9.
13. Panicker SG, Mandal AK, Reddy AB, Gothwal VK, Hasnain SE. Correlations of genotype with phenotype in Indian patients with primary congenital glaucoma. *Invest Ophthalmol Vis Sci*. 2004;45:1149–1156.
14. Libby RT, Smith RS, Savinova OV, et al. Modification of ocular defects in mouse developmental glaucoma models by tyrosinase. *Science*. 2003;299:1578–1581.
15. Hubbard T, Barker D, Birney E, et al. The Ensembl genome database project. *Nucleic Acids Res*. 2002;30:38–41.
16. Riazuddin S, Castelein CM, Ahmed ZM, et al. Dominant modifier DFNM1 suppresses recessive deafness DFNB26. *Nat Genet*. 2000;26:431–434.
17. Bykhovskaya Y, Yang H, Taylor K, et al. Modifier locus for mitochondrial DNA disease: linkage and linkage disequilibrium mapping of a nuclear modifier gene for maternally inherited deafness. *Genet Med*. 2001;3:177–180.
18. Jansson I, Stoilov I, Sarfarazi M, Schenkman JB. Effect of two mutations of human CYP1B1, G61E, R469W, on stability and endogenous steroid substrate metabolism. *Pharmacogenetics*. 2001;11:793–801.
19. van Dorp DB, Delleman JW, Loewer-Sieger DH. Oculocutaneous albinism and anterior chambre cleavage malformations: not a coincidence. *Clin Genet*. 1984;26:440–444.
20. Larkin DF, O'Donoghue HN. Developmental glaucoma in oculocutaneous albinism. *Ophthalmic Paediatr Genet*. 1988;9:1–4.
21. Weidner C, Reperant J, Desroches AM, Miceli D, Rio JP. Course of the degeneration of the primary visual system in albino quails with glaucoma. *Can R Acad Sci*. 1986;303:397–402.
22. Dkhissi O, Chanut E, Versaux-Botteri C, Minvielle F, Trouvin JH, Nguyen-Legros J. Changes in retinal dopaminergic cells and dopamine rhythmic metabolism during the development of a glaucoma-like disorder in quails. *Invest Ophthalmol Vis Sci*. 1996;37:2335–2344.