

Glaucoma (Primary Congenital), *CYP1B1* Sequencing

TO DIAGNOSE OR DETERMINE CARRIER STATUS FOR PRIMARY CONGENITAL GLAUCOMA

Disease Overview

- Characteristics include: high intraocular pressure, globe enlargement and edema, corneal opacification, thinning of anterior sclera, iris atrophy, anomalous deep anterior chamber, photophobia, blepharospasm, and excessive tearing.
- Disease manifests in infancy and is bilateral in 70 percent of individuals.
- Depending on timing of treatment, those affected may have reduced visual acuity and restricted visual fields; without treatment, blindness occurs.
- Accounts for 4 percent of childhood blindness.

Epidemiology

Occurs in one in 5,000–20,000 individuals from Western countries, one in 2,500 Middle Easterners, one in 3,300 Andhra Pradesh Indians, and one in 1,250 Slovakian Gypsies; variable in other ethnicities.

Genetics

- Three loci have been linked to primary congenital glaucoma, yet only one of the causative genes, Cytochrome P4501B1 (*CYP1B1*), has been identified.
- *CYP1B1* mutations are inherited in an autosomal recessive manner and can be detected in 20–100 percent of familial cases and 10–15 percent of isolated cases.
- *CYP1B1* mutations may also be present in patients with Peters anomaly, Rieger anomaly, or malformations in the anterior chamber of the eye.

Indications for Ordering

- To confirm a clinical diagnosis of primary congenital glaucoma.
- Carrier testing for family members of individuals with primary congenital glaucoma or an identified *CYP1B1* mutation.
- Prenatal diagnosis of subsequent pregnancies of a couple who has a child with identified *CYP1B1* mutation(s).

Interpretation

- The absence of detectable *CYP1B1* mutations does not exclude being affected with, or a carrier of, disease.
- Individuals with one detectable *CYP1B1* mutation are at least carriers.
- Individuals with two *CYP1B1* mutations on opposite chromosomes are predicted to be affected.
- Gene sequencing may reveal novel mutation(s); thus, the determination of clinical significance (benign or deleterious) may be unclear.

Methodology

- Bidirectional sequencing of entire coding region of *CYP1B1*, including five prime untranslated region and intron-exon boundaries.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity is 20–100 percent for familial cases, 10–15 percent for isolated cases.

Limitations

- Large gene deletions/duplications and deep intronic mutations will not be identified.
- Rare diagnostic errors may occur due to primer-site mutations.

References

1. Stoilov 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;62:573–84.
2. Online GeneTests: Primary Congenital Glaucoma. www.genetests.org (accessed on May 12, 2009).
3. Chavarria-Soley G, et al. Primary congenital glaucoma and Rieger's anomaly: extended haplotypes reveal founder effects for eight distinct *CYP1B1* mutations. *Molecular Vision* 2006;12:523–31.
4. Sarfarazi M, et al. Genetics and biochemistry of primary congenital glaucoma. *Ophthalmol Clin North Am* 2003;16:543–54.

Test Information

0051476 Glaucoma (Primary Congenital), *CYP11B* Sequencing

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.