



Crigler-Najjar Syndrome: Mutation Analysis of *UGT1A1*

Clinical Features:

Crigler-Najjar syndromes (CN) are inborn disorders of the liver metabolism of bilirubin characterized by non-hemolytic unconjugated hyperbilirubinemia. CN are classified into two types based on the bilirubin levels, the presence of kernicterus and the reduction of the bilirubin levels upon administration of Phenobarbital or other enzyme-inducing agents (1). Crigler-Najjar syndrome, type I (CN-I) [OMIM # 218800] is characterized by serum bilirubin more than 25 times that of the normal level. Persistent elevated unconjugated bilirubin is present in the neonatal period in individuals with CN-1, which can cause kernicterus and death in infancy or childhood. Phototherapy is the current long-term therapy for CN-1, with liver transplantation being the only definitive treatment. Crigler-Najjar syndrome, type II (CN-II) [OMIM #606785] is characterized by serum bilirubin 6-25 times that of the normal level. CN-II is rarely associated with kernicterus and patients typically respond to Phenobarbital treatment (2). Mild hyperbilirubinemia is associated with Gilbert Syndrome.

Molecular Genetics:

Mutations in the UDP-Glycosyltransferase 1 Family, Polypeptide A1 (*UGT1A1*) gene [OMIM #191740] have been identified in patients with CN. *UGT1A1* encodes the bilirubin uridine diphospho-glucuronosyltransferase (B-UGT) which is the enzyme that catalyzes the glucuronidation of bilirubin. CN-1 is due to the total absence of hepatic B-UGT activity, and B-UGT activity in CN-II is usually less than 10% of normal (2). The *UGT1A1* gene maps to 2q37.1. It has 4 coding exons, and to date missense, nonsense, frameshift and splice site mutations, and small insertions and deletions have been described (3). Large deletions (>20bp) are rare (4).

Inheritance:

The incidence of CN is estimated to be approximately one in a million live births (5). CN-1 is inherited in an autosomal recessive pattern. Parents of an affected child are likely carriers. Recurrence risk for carrier parents is 25%. CN-II is generally considered to be inherited in an autosomal recessive pattern but autosomal dominant inheritance has also been reported (6).

Test methods:

We offer full gene sequencing of all 4 coding exons and intron/exon boundaries. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Note: *UGT1A1* sequencing analysis will also detect the *UGT1A1*28* variant in the promoter region of the *UGT1A1* gene, if present. This variant, when present in the homozygous state, is associated with Gilbert syndrome.

[UGT1A1 sequencing and deletion/duplication analysis](#)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$875
CPT codes:	81403, 81404
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Costa E. Hematologically important mutations: bilirubin UDP-glucuronosyltransferase gene mutations in Gilbert and Crigler-Najjar syndromes. *Blood Cells Mol Dis* 2006; 36: 77-80.
2. Zmetáková I, Ferák V, Minárik G et al. Identification of the deletions in the UGT1A1 gene of the patients with Crigler-Najjar syndrome type I from Slovakia. *Gen Physiol Biophys* 2007; 26: 306-310.
3. Kaplan M, Hammerman C. Bilirubin and the Genome: the hereditary basis of unconjugated neonatal hyperbilirubinemia. *Current Pharmacogenomics* 2005; 3: 21-42.
4. Petit FM, Hébert M, Gajdos V et al. Large deletion in UGT1A1 gene encompassing the promoter and the exon 1 responsible for Crigler-Najjar type I syndrome. *Haematologica* 2008; 93: 1590-1591.
5. Labrune P. Crigler-Najjar Syndrome. *Orphanet Encyclopedia*, 2004.
6. Koiwai O, Aono S, Adachi Y et al. Crigler-Najjar syndrome type II is inherited both as a dominant and as a recessive trait. *Hum Mol Genet* 1996; 5: 645-647.

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