THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

UGT1A1 Genotyping/Gilbert Syndrome

Clinical Features:

- **Gilbert syndrome** – Gilbert syndrome is characterized by mild, chronic, unconjugated hyperbilirubinemia in the absence of liver disease or overt hemolysis and is found in approximately 3-10% of the general population. The diagnosis of this disorder is made on the observation of elevated unconjugated bilirubin levels and normal liver function. The importance of the diagnosis of this benign syndrome is to rule out more serious liver disease as the underlying cause of the hyperbilirubinemia. However, as the diagnosis is largely one of exclusion, it is sometimes difficult to dispel lingering fears of serious liver disease, causing patients unwarranted anxiety.

- **Irinotecan metabolism** – Irinotecan is an anti-cancer agent that is used for the treatment of metastatic carcinoma of the colon or rectum. Although it prolongs survival, it causes severe (grade 3-4) diarrhea and neutropenia in approximately 20-35% of patients treated. The ability to predict patients who will eventually suffer these potentially fatal toxicities is an important consideration when using irinotecan.

Inheritance:

Gilbert syndrome is generally considered to be an autosomal recessive disorder. However there have been cases of heterozygosity reported in patients with Gilbert syndrome, particularly in the Asian population.

Molecular Genetics:

- **Gilbert syndrome** – Individuals with Gilbert syndrome have a reduced level of hepatic bilirubin UDP-glucuronosyltransferase 1A1 (*UGT1A1*), the enzyme necessary for the conjugation of bilirubin. This enzyme is encoded for by the *UGT1A1* gene on chromosome 2q37. A polymorphism in the promoter region of the *UGT1A1* gene has been identified in the majority of Caucasian individuals with Gilbert syndrome (80-100%). These individuals are homozygous for two extra bases (TA) in the promoter region of the gene and have an $A(TA)_7TAA$ sequence rather than an $A(TA)_6TAA$ sequence (1, 2). This change is associated with reduced expression of the *UGT1A1* gene and thereby reduced levels of the UGT1A1 protein. The frequency of the $A(TA)_7TAA$ allele is approximately 40% in the general population. The $A(TA)_7TAA$ allele is also known as UGT1A1*28.

  A missense change in the *UGT1A1* gene, G71R, has been identified in approximately 30-40% of Asian individuals with neonatal hyperbilirubinemia and has been implicated in Gilbert syndrome in this population (3). This change is also associated with a decreased expression of the *UGT1A1* gene. The frequency of the G71R allele is approximately 10% in the general Asian population. The G71R allele is also known as UGT1A1*6.

- **Irinotecan metabolism** – Irinotecan is converted in the liver to its active metabolite, SN-38, which subsequently gets conjugated to its glucuronide, SN-38G that is excreted from the body. Decreased levels of glucuronidation results in elevated amounts of SN-38 that is responsible for the severe diarrhea and neutropenia phenotypes in patients. *UGT1A1* is involved in the glucuronidation of SN-38 to its glucuronide and the $A(TA)_7TAA$ allele has been associated with decreased glucuronidation. Individuals homozygous for the $A(TA)_7TAA$ allele are at an elevated risk of developing toxicity phenotypes with irinotecan treatment (4, 5). The association of the G71R change with Irinotecan metabolism has not been well studied to date.

Additional Resources:

Gilberts Web
Email: general@gilbertsweb.co.uk
www.gilbertsweb.co.uk

Test methods:

- **Gilbert syndrome** – We offer genotype analysis of the A(TA)$_7$TAA allele by PCR and sizing by capillary electrophoresis that can discriminate between the A(TA)$_7$TAA and A(TA)$_6$TAA alleles. Any samples that are not homozygous for the A(TA)$_7$TAA allele will also be tested for the G71R polymorphism.

  UGT1A1 genotype analysis for Gilbert syndrome

Sample specifications:	3-10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81350
Turn-around time:	2 weeks

- **Irinotecan metabolism** – We offer genotype analysis of the A(TA)$_7$TAA allele by PCR and sizing by capillary electrophoresis that can discriminate between the A(TA)$_7$TAA and A(TA)$_6$TAA alleles.

  UGT1A1 A(TA)$_7$TAA genotype analysis for irinotecan dosing

Sample specifications:	3-10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81350
Turn-around time:	≤ 7 days

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested.

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

References:

1. Bosma PJ, Chowdhury JR, Bakker C et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med 1995: 333: 1171-1175.
2. Monaghan G, Ryan M, Seddon R et al. Genetic variation in bilirubin UPD-glucuronosyltransferase gene promoter and Gilbert's syndrome. Lancet 1996: 347: 578-581.
3. Akaba K, Kimura T, Sasaki A et al. Neonatal hyperbilirubinemia and a common mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene in Japanese. J Hum Genet 1999: 44: 22-25.
4. Innocenti F, Undevia SD, Iyer L et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004: 22: 1382-1388.
5. Iyer L, Das S, Janisch L et al. UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2002: 2: 43-47.

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