

UGT1A1 Gene Analysis

Variants in the *UGT1A1* gene cause decreased production of the functional enzyme, UDP-glucuronosyltransferase, responsible for bilirubin metabolism leading to hyperbilirubinemia. The severity of the functional deficiency of hepatic UGT1A1 is determined by the genetic variant(s); thus, the resulting phenotypic spectrum is variable. Crigler-Najjar syndrome is a rare, autosomal recessive disorder resulting from severe functional deficiency of hepatic UGT1A1 and characterized by intermediate-severe hyperbilirubinemia, jaundice, and risk for kernicterus. Gilbert syndrome is a common inherited condition resulting from a mild decrease in UGT1A1 activity, and individuals may be asymptomatic or have mild, fluctuating hyperbilirubinemia and intermittent jaundice.

The UGT1A1 enzyme is also involved in the metabolism of certain drugs, including irinotecan, a topoisomerase I inhibitor, and atazanavir, an antiretroviral protease inhibitor. *UGT1A1* variants resulting in enzyme deficiency are associated with an increased risk for drug toxicity.

Disease Overview

Incidence

- Gilbert syndrome: 3-7% of U.S. population
- Crigler-Najjar syndrome: 1/million

Symptoms

- Inherited unconjugated hyperbilirubinemia without hemolytic anemia or liver dysfunction
- Spectrum of clinical phenotypes differentiated by level of residual hepatic uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme activity, serum bilirubin levels, and response to phenobarbital loading
- Crigler-Najjar syndrome type I (MIM #218800)
 - Most severe phenotype resulting from absence/near absence of hepatic UGT1A1 activity
 - Severe hyperbilirubinemia, jaundice, and risk for kernicterus
 - Refractory to phenobarbital
- Crigler-Najjar syndrome type II (MIM #606785)
 - Greatly reduced hepatic UGT1A1 activity (typically <10% of normal)
 - Intermediate hyperbilirubinemia jaundice, and low risk for kernicterus
 - Responsive to phenobarbital loading
- Gilbert syndrome (MIM #143500)
 - Decreased UGT1A1 activity
 - Mild, fluctuating hyperbilirubinemia
 - Commonly asymptomatic, jaundice may be intermittent
 - Not associated with kernicterus

Pathophysiology

- UGT1A1 enzyme metabolizes endogenous substances (eg, bilirubin) and drugs (eg, irinotecan)
- Irinotecan (CPT-11, Camptosar, Onivyde) is a topoisomerase I inhibitor
 - Interrupts DNA replication in cancer cells, causing cell death
 - Prodrug irinotecan is metabolized to active metabolite SN-38, and inactivated by UGT1A1
 - Decreased UGT1A1 activity reduces ability to metabolize SN-38 to inactive form

Tests to Consider

UGT1A1 Sequencing 3001755

Method: Polymerase Chain Reaction/Sequencing

- Bidirectional sequencing of the *UGT1A1* coding regions, intron/exon boundaries and the polymorphic (TA)_nTAA repeats within the promoter region
- Indications for Ordering:
 - Confirms suspected diagnosis of Gilbert syndrome or Crigler-Najjar syndrome
 - Dosage planning for individuals who will receive high-dose irinotecan, have a history of irinotecan sensitivity, or experience neutropenia while receiving irinotecan
 - Assesses risk of bilirubin-related discontinuation of atazanavir

UDP Glucuronosyltransferase 1A1 (UGT1A1) Genotyping 0051332

Method: Polymerase Chain Reaction/Fragment Analysis

- Polymerase chain reaction/fragment analysis to assess the polymorphic *UGT1A1* (TA)_nTAA promoter repeats
- Alleles tested:
 - *1 (TA)₆
 - *36 (TA)₅
 - *28 (TA)₇
 - *37 (TA)₈

Indications for Ordering:

- Dosage planning for individuals who will receive high-dose irinotecan, have a history of irinotecan sensitivity, or experience neutropenia while receiving irinotecan
- Confirms suspected diagnosis of Gilbert syndrome

- Atazanavir (Reyataz), an antiretroviral protease inhibitor, inhibits hepatic UGT1A1

Pharmacogenetic Indications

- Irinotecan
 - Approved for treatment of metastatic colorectal cancer
 - May be used in metastatic lung, brain, and breast cancer
 - Irinotecan is associated with severe diarrhea and neutropenia in 20-35% of individuals
 - Toxicity of irinotecan is associated with specific *UGT1A1* genotype variants in patients receiving high-dose
- Atazanavir
 - Approved human immunodeficiency virus (HIV) type 1 protease inhibitor
 - Risk for premature bilirubin-related discontinuation associated with *UGT1A1* genotype
 - [CPIC Guideline for Atazanavir and UGT1A1](#) is available.

Genetics

Gene

UGT1A1

Inheritance

Autosomal recessive for Gilbert and Crigler-Najjar syndromes; de novo variants are rare

Variants

- Functional deficiency of UGT1A1 varies depending on specific genetic variant(s)
- *UGT1A1* pathogenic variants in coding region
 - Homozygosity or compound heterozygosity commonly results in Crigler-Najjar syndrome
 - Homozygosity for the mildly pathogenic variant *UGT1A1**6 (rs4148323, c.211G>A, p.Gly71Arg) is a common cause of Gilbert syndrome in East Asians
- Polymorphic TA repeats in the *UGT1A1* promoter region, (TA)_nTAA, rs3064744, NC_000002.11:g.234668881_234668882TA[n], (HGVS, n=5, 6, 7, or 8)
 - 6 is the most common number of repeats, also known as *UGT1A1**1 (TA)₆
 - Homozygosity for 7 repeats, *28 (TA)₇, is a common cause of Gilbert in Caucasians/African Americans, with reduced expression of UGT1A1 to ~60-80% of the wild type¹

Test Interpretation

Sensitivity/Specificity

- Analytical sensitivity and specificity: >99%
- Clinical sensitivity/specificity: estimated risk of irinotecan toxicity by genotype in Caucasian patients with colorectal cancer²

TA Genotype	Diarrhea Risk	Neutropenia Risk	Irinotecan Dosing
6/6 (*1/*1)	14.7%	10.7%	Standard
6/7 (*1/*28)	OR=1.20	OR=1.90	Based on clinical findings
7/7 (*28/*28)	OR=1.84	OR=4.79	Dose reduction recommended

OR, odds ratio

- Risks for bilirubin-related atazanavir discontinuation by *UGT1A1* phenotype³

UGT1A1 Phenotype	Common Genotypes	Risk for Bilirubin-Related Discontinuation of Atazanavir
Poor metabolizer	*28/*28, *28/*37, *37/*37	20-60%
Intermediate metabolizer	*1/*28, *1/*37, *36/*28, *36/*37	Less than 5%
Extensive metabolizer	*1/*1, *1/*36, *36/*36	Less than 5%

Limitations

Gilbert and Crigler-Najjar Syndromes (*UGT1A1*) Sequencing

- Diagnostic errors can occur due to rare sequence variations
- *UGT1A1* regulatory region variants other than the (TA)_nTAA promoter polymorphisms, *1 TA(6), *36 TA(5), *28 TA(7), and *37 TA(8), will not be analyzed
- Deep intronic variants, large deletions/duplications/insertions, and gene conversion events will not be detected
- Variants of uncertain clinical significance within the *UGT1A1* coding region will not be reported for pharmacogenetic indications
- Genetic and nongenetic factors other than *UGT1A1*, may contribute to irinotecan toxicity and efficacy, and risk for bilirubin-related discontinuation of atazanavir

UDP Glucuronosyltransferase 1A1 (*UGT1A1*) Genotyping

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- Genetic and nongenetic factors other than *UGT1A1* may contribute to irinotecan toxicity and efficacy, and risk for bilirubin-related discontinuation of atazanavir
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References

1. Beutler E, Gelbart T, Demina A. [Racial variability in the UDP-glucuronosyltransferase 1 \(*UGT1A1*\) promoter: a balanced polymorphism for regulation of bilirubin metabolism?](#) Proc Natl Acad Sci U S A. 1998;95(14):8170-8174. PubMed
2. Liu X, Cheng D, Kuang Q, et al. [Association of *UGT1A1**28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians.](#) Pharmacogenomics J. 2014;14(2):120-129. PubMed
3. Gammal RS, Court MH, Haidar CE, et al. [Clinical Pharmacogenetics Implementation Consortium \(CPIC\) guideline for *UGT1A1* and atazanavir prescribing.](#) Clin Pharmacol Ther. 2016;99(4):363-369. PubMed

Additional Resources

Clinical Pharmacogenetics Implementation Consortium. [CPIC guidelines](#). [Last modified: Nov 2018; Accessed: Feb 2019]

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