UGT1A1 Gene Analysis

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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 uridine diphosphate glucuronosyltransferase (UGT) 1A1 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 United States 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 UGT1A1 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 the ability to metabolize SN-38 into its inactive form.
- Atazanavir (Reyataz), an antiretroviral protease inhibitor, inhibits hepatic UGT1A1.

Featured ARUP Testing

UGT1A1 Sequencing 3004386

Method: Massively Parallel Sequencing

Massively parallel sequencing of the *UGT1A1* coding regions, intron/exon boundaries and the polymorphic (TA)nTAA repeats within the promoter region

- Use to confirm suspected diagnosis of Gilbert syndrome or Crigler-Najjar syndrome
- Use for dosage planning for individuals who will receive high-dose irinotecan, have a history of irinotecan sensitivity, or experience neutropenia while receiving irinotecan
- Use to assess risk of bilirubin-related discontinuation of atazanavir

UDP Glucuronosyltransferase 1A1 (UGT1A1) Genotyping 0051332

Method: Polymerase Chain Reaction (PCR)/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
- Use for dosage planning for individuals who will receive high-dose irinotecan, have a history of irinotecan sensitivity, or experience neutropenia while receiving irinotecan
- Use to confirm suspected diagnosis of Gilbert syndrome

For more information about combined *DPYD* and *UGT1A1* testing, refer to the Dihydropyrimidine Dehydrogenase (*DPYD*) and UPD Glucuronosyltransferase 1A1 (*UGT1A1*) Genotyping Test Fact Sheet.

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 a 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 (NM_000463), promoter (NC_000002)

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 syndrome in Whites and African Americans/Blacks, with reduced expression of UGT1A1 to ~60-80% of the wild type[1]

Test Interpretation

Clinical Sensitivity

Estimated risk of irinotecan toxicity by genotype in White patients with colorectal cancer[2]

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* phenotype[3]

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%

UGT1A1 Phenotype	Common Genotypes	Risk for Bilirubin-Related Discontinuation of Atazanavir
Extensive metabolizer	**1/*1*, **1/*36*, **36/*36*	Less than 5%

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions, 1-10 bp	93.8	84.3-98.2
Deletions, 11-44 bp	99.9	87.8-100
Insertions, 1-10 bp	94.8	86.8-98.5
Insertions, 11-23 bp	99.9	62.1-100

[a]Genes included in this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

UGT1A1 Sequencing

- The following will not be evaluated:
  - Variants outside the coding regions, intron-exon boundaries, or (TA)nTAA promoter region of UGT1A1
  - Regulatory region and deep intronic variants
  - Noncoding transcripts
  - Large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
- Diagnostic errors can occur due to rare sequence variations.
- Variants of uncertain clinical significance within the *UGT1A1* coding region will not be reported for pharmacogenetic indications.
- Genetic factors other than *UGT1A1* and nongenetic factors may contribute to irinotecan toxicity and efficacy and risk for bilirubin-related discontinuation of atazanavir.

UDP Glucuronosyltransferase 1A1 (*UGT1A1*) Genotyping

- Variants other than the (TA)nTAA promoter polymorphisms **1* TA(6), **36* TA(5), **28* TA(7), and **37* TA(8) will not be detected.
- Genetic and nongenetic factors other than *UGT1A1* may contribute to irinotecan toxicity and efficacy, and risk for bilirubin-related discontinuation of atazanavir.
- Diagnostic errors can occur due to rare sequence variations.

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.

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.

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.

Additional Resources

Clinical Pharmacogenetics Implementation Consortium. CPIC guidelines. Updated Mar 2021; accessed Oct 2021.

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