SCHOOL OF MEDICINE
INDIANA UNIVERSITY

Gilbert syndrome *UGT1A1* Genotyping

For detection of UGT1A1 *variants in Gilbert syndrome*

Clinical Background

Gilbert syndrome is a relatively mild condition characterized by periods of elevated levels of a toxic substance called bilirubin in the blood (hyperbilirubinemia). Bilirubin, which has an orange-yellow tint, is produced when red blood cells are broken down. This substance is removed from the body only after it undergoes a chemical reaction in the liver, which converts the toxic form of bilirubin (unconjugated bilirubin) to a nontoxic form called conjugated bilirubin. People with Gilbert syndrome have a buildup of unconjugated bilirubin in their blood (unconjugated hyperbilirubinemia). In affected individuals, bilirubin levels fluctuate and very rarely increase to levels that cause jaundice, which is yellowing of the skin and whites of the eyes.

Epidemiology

- Gilbert syndrome is a common condition that is estimated to affect 3 to 7 percent of Americans.
- *UGT1A1* variant frequency is ethnicity dependent.

Genetics

- The *UGT1A1* gene is located on chromosome 2q37.1.
- Inheritance is autosomal recessive.

Indications for Ordering

- This test is intended to identify the UGT1A1*28 (g.4963_4964[7]), UGT1A1*36 (g.4963_4964[5]), and UGT1A1*37 (g.4963_4964[8]) variants in *UGT1A1* from genomic DNA. Information about these variants may be used as an aid to clinicians for confirming a diagnosis of Gilbert syndrome.

Interpretation

- If no *UGT1A1* variants are detected, this suggests *1/*1 and normal enzymatic activity.
- If one decreased functional *UGT1A1* variant is detected, this suggests an unaffected carrier. This result does not rule out a diagnosis of Gilbert syndrome. The risk for mutations that cause Gilbert other than the ones tested depends greatly on family history, clinical presentation, and

ethnicity. If a diagnosis of Gilbert syndrome is suspected, additional testing such as *UGT1A1* gene sequencing or deletion/duplication analysis should be performed.

- If two non-functional variants are present on opposite allele, this predicts low UGT1A1 enzymatic activity and a diagnosis of Gilbert syndrome.
- Genotype results should be interpreted in context of the individual clinical situation. Consultation with a clinical genetics professional is recommended.

Methodology

- Polymerase chain reaction (PCR) and fragment analysis with capillary electrophoresis

Variants in *UGT1A1* Assay

Allele	Variant	dbSNP	Predicted enzyme activity
*1	$(TA)_6$ repeats	N/A	Normal
*28	$(TA)_7$ repeats	rs8175347	Decreased
*36	$(TA)_5$ repeats	rs8175347	Increased
*37	$(TA)_8$ repeats	rs8175347	Decreased