Warde Medical Laboratory

LABORATORY REPORT

QC ACCOUNT (WARDE)
300 W. TEXTILE
ANN ARBOR MI 48108

EXAMPLE, REPORT W
WX0000003827 M 07/08/1968 56 Y

Referral Testing

Collected: 03/11/2025 08:17 Received: 03/11/2025 08:17

Test Name	Result	Flag	Ref-Ranges	Units	Site

Hereditary Hemolytic Anemia Panel Sequencing

Her. Hemolytic Anemia Sequencing Specimen	Whole Blood	ARRL
Her. Hemolytic Anemia Sequencing Interp	See Note	ARRL

RESULT
One mildly pathogenic variant was detected in the UGT1A1 gene.

PATHOGENIC MILD VARIANT
Gene: UGT1A1 (NC_000002.11)
Nucleic Acid Change: g.234668881TA[8]; Heterozygous
Commonly Known As: (TA)7 or *28 allele
Inheritance: Autosomal Recessive

INTERPRETATION
One copy of the mildly pathogenic variant, *28 (TA)7 promoter variant, was detected in the UGT1A1 gene by massively parallel sequencing. Pathogenic variants in UGT1A1 are inherited in an autosomal recessive manner and are associated with type I and type II Crigler-Najjar syndromes (MIM: 218800, 606785) and mild hyperbilirubinemia, known as Gilbert syndrome (MIM: 143500; OMIM (R)). Heterozygosity for the *28 (TA)7 promoter variant is associated with partially decreased UGT1A1 enzyme level but carriers are not expected to have hyperbilirubinemia. This result decreases the likelihood of, but does not exclude a diagnosis of Gilbert or Crigler-Najjar syndromes. Clinical presentation may be influenced by other genetic modifiers or co-existing conditions.
This genotype may impact the metabolism of certain drugs and dosing should be based on clinical findings. Guidelines for genotype-based dosing recommendations published by the Clinical Pharmacogenetic Implementation Consortium (CPIC) are located at:
https://cpicpgx.org/guidelines/.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and

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limitations of this test.

Evidence for variant classification:
The UGT1A1 TATA box commonly has 6 TA repeats; however, there
can be 5 TA repeats, 7 TA repeats, or less commonly, 8 and 9 TA
repeats (Barbarino 2014). In vitro studies have shown that
UGT1A1 promoter expression decreases as the number of TA repeats
increases (Beutler 1998). Genotypes that are homozygous for
(TA)7, homozygous for (TA)8, or compound heterozygotes for
(TA)7, (TA)8, or (TA)9 cause reduced expression of UGT1A1 and
are associated with Gilbert syndrome, which is characterized by
increased bilirubin levels, and may have a neonatal appearance
of hereditary spherocytosis (Bosma 1995, Iolascon 1998, Nikolac
2008, Ostanek 2007). Individuals who are heterozygous for the
(TA)7 *28 promoter variant may have an increased risk for drug
toxicity when treated with irinotecan (Marcuello 2004, Riera
2018). Individuals who are homozygous for (TA)7 or compound
heterozygous for more than 6 TA repeats may experience an
increased incidence of atazanavir-associated hyperbilirubinemia
(Gammal 2016).

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of
medical screening and management.

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS
with sufficient confidence in this sample due to technical
limitations: None

REFERENCES
Barbarino JM et al. PharmGKB summary: very important
pharmacogene information for UGT1A1. Pharmacogenet
Genomics.

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2014 24:177-183. PMID: 24492252
Beutler E et al. 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 95:8170-8174. PMID: 9653159
Bosma PJ 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. PMID: 7565971
Gammal RS et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. Clin Pharmacol Ther. 2016 99:363-369. PMID: 26417955
Iolascon A et al. UGT1 promoter polymorphism accounts for increased neonatal appearance of hereditary spherocytosis. Blood. 1998 91:1093. PMID: 9446675
Marcuello E et al. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br J
Cancer. 2004 91:678-682. PMID: 15280927
Nikolac N et al. Rare TA repeats in promoter TATA box of the UDP
glucuronosyltranferase (UGT1A1) gene in Croatian subjects. Clin
Chem Lab Med. 2008 46:174-178. PMID: 18324905
OMIM(R) Copyright (C) 1996 - Present year, Johns Hopkins University All rights reserved.
Ostanek B et al. UGT1A1(TA)n promoter polymorphism--a new case
of a (TA)8 allele in Caucasians. Blood Cells Mol Dis. 2007 38:78-82. PMID: 17196409
Riera P et al. Relevance of CYP3A4*20, UGT1A1*37 and UGT1A1*28
variants in irinotecan-induced severe toxicity. Br J Clin Pharmacol. 2018 84:1389-1392. PMID: 29504153

This result has been reviewed and approved by Ganna Shestakova,
M.D., Ph.D.
BACKGROUND INFORMATION: Hereditary Hemolytic Anemia Panel, Sequencing

CHARACTERISTICS: Hereditary Hemolytic Anemia (HHA) comprises a diverse group of heterogeneous disorders characterized by premature red blood cell (RBC) destruction and anemia due to intrinsic RBC defects. Individuals with

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HHA have decreased hemoglobin concentration, hematocrit and RBC count. Additional characteristics include blood smear abnormalities, such as spherocytes, acanthocytes, schistocytes, bite cells, stomatocytes, polychromasia and target cells. Presentation may include hyperbilirubinemia or jaundice due to red cell hemolysis. Causes of HHA involve RBC membrane defects (eg, hereditary spherocytosis), RBC enzymopathies (eg, glucose-6-phosphate dehydrogenase or pyruvate kinase deficiencies) and hemoglobinopathies.

EPIDEMIOLOGY: Incidence is estimated at 1:500-1:1,100.

CAUSE: Pathogenic germline variants in genes associated with defects in the RBC membrane proteins, deficiencies of RBC enzymes, or hemoglobinopathies.

INHERITANCE: Varies by gene; autosomal dominant, autosomal recessive or X-linked recessive.

GENES TESTED: AK1, ALDOA, ANK1, CDAN1, CYB5R3, EPB41, EPB42, G6PD, GCLC, GPI, GSR, GSS, HK1, NT5C3A, PFKM, PGK1, PIEZO1, PKLR, SEC23B, SLC4A1, SLCO1B1, SLCO1B3, SPTA1, SPTB, TPI1, UGT1A1, UGT1A6, UGT1A7

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a heritable form of hemolytic anemia. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. The genes of the alpha- and beta-globin clusters are not analyzed. Regulatory region variants and deep intronic variants will not be identified. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases,

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variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation or recently received a blood transfusion. Non-coding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.
Performed By: ARUP Laboratories
500 Chipeta Way
Salt Lake City, UT 84108
Laboratory Director: Jonathan R. Genzen, MD, PhD
CLIA Number: 46D0523979

Reported Date: 03/11/2025 08:19 HHAPS

Performing Site:
ARRL: ARUP REFERENCE LAB 500 Chipeta Way Salt Lake City UT 841081221