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MEDGENOME

DNA TEST REPORT – MEDGENOME LABORATORIES

Full Name/ Ref No:	**Mrs. Amrisha Parathalingam**	**Order ID/ Sample ID:**	**1311079/9161409**
Date of Birth / Age:	42 years	**Gender:**	Female
Referring Clinician:	Dr. Mahendra Perera, Aegle Omics Private Limited - Colombo	**Specimen Type:**	EDTA blood (5 tubes)
		Date of Sample Collection:	21-05-2025
Date of order:	26-05-2025	**Date of Sample Receipt:**	24-05-2025
Test Requested	Irinotecan toxicity testing (MGM551)	**Date of Report:**	09-06-2025

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

The subject has been tested for variations in the *uridine diphosphate glucuronosyltransferase (UGT) 1A1* (*UGT1A1*) gene (*6 and *28) for irinotecan toxicity testing.

RESULTS

Gene	Variation tested	dbSNP ID	Variation status	Clinical Relevance
UGT1A1	c.-53_-52insTA; *UGT1A1*28*	rs3064744	**Present Homozygous (*UGT1A1*28- Two copies*)**	YES
	c.211G>A; p. (Gly71Arg); *UGT1A1*6*	rs4148323	Absent	NIL

VARIANT INTERPRETATION AND RECOMMENDATION

A homozygous 2 bp insertion of TA [c.-53_-52insTA], leading to 7 TA repeats ($A(TA)_7TAA$) in the promoter region of ***UGT1A1*** gene was detected in this patient sample. The UGT1A1 promoter region with six TA repeats [$A(TA)_6TAA$] is considered normal, while TA repeats of seven (***UGT1A1*28***) result in decreased transcriptional activity of UGT1A1. The ***UGT1A1*28*** allele has been assigned as a decreased function allele by CPIC (The Clinical Pharmacogenetics Implementation Consortium). **According to PharmGKB, individuals carrying two copies of *UGT1A1*28* allele may have increased likelihood of neutropenia and increased severity of diarrhea when treated with irinotecan-based regimens as compared to patients with two normal function alleles. Individuals carrying UGT1A1*28 allele may require a decreased dose of irinotecan compared to individuals carrying two normal function alleles.** However, conflicting evidence has been reported. [1-3] Other genetic and clinical factors may also influence irinotecan related neutropenia and dose requitements.

BACKGROUND INFORMATION

Irinotecan hydrochloride is one of the key anticancer drugs in chemotherapy for several cancers including colorectal cancer, lung cancer, gastric cancer, and gynecologic cancers. The *UGT1A1* gene belongs to a family of genes that provide instructions for producing enzymes called UDP-glucuronosyltransferases which catalyzes the glucuronidation reaction. The protein produced from the *UGT1A1* gene, converts the active metabolite of Irinotecan, SN-38 (7-ethyl-10-hydroxycamptothecin), to its inactive form SN-38 glucuronide (SN-38G) and detoxifies it. Patients who harbour UGT1A1 poymorphisms exhibit higher serum concentrations of SN-38 than SN-38G due to defective detoxification and are considered poor metabolizers of Irinotecan. Such patients experience severe toxicities after administration of the drug. The most common variations reported in UGT1A1 are *UGT1A1*6* (Gly71Arg) and *UGT1A1*28*, which is characterized by the presence of $A(TA)_7TAA$ sequence in the promoter region [3-5].

METHODOLOGY

Targeted gene sequencing: Genomic DNA was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean >80- 100X coverage on Illumina sequencing platform. We follow the GATK best practices framework for identification of variants in the sample using Sentieon (v201808.07). [6] The sequences obtained are aligned to human reference genome (GRCh38.p13) using Sentieon aligner [6, 7] and analyzed using Sentieon for removing duplicates, recalibration and re-alignment of indels. [6] Sentieon haplotype caller has been used to identify variants which are relevant to the clinical indication. Gene annotation of the variants is performed using VEP program [8] against the Ensembl release 99 human gene model. [9]

GUIDELINES FOR CLINICAL INTERPRETATION

The Pharmacogenomics Knowledge Base (PharmGKB) [10] is a comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers. PharmGKB displays genotype, molecular, and clinical knowledge integrated into pathway representations and Very Important Pharmacogene (VIP) summaries with links to additional external resources. Users can search and browse the knowledgebase by genes, variants, drugs, diseases, and pathways.

LIMITATIONS

- Only clinically relevant alleles in *UGT1A1* (*6 and *28) and irinotecan toxicity according to PharmGkb are assayed in this test.
- Genetic testing is highly accurate. Rarely, inaccurate results may occur for various reasons. These reasons include, but are not limited to mislabelled samples, inaccurate reporting of clinical/medical information, rare technical errors or unusual circumstances such as bone marrow transplantation, blood transfusion; or the presence of change(s) in such a small percentage of cells that may not be detectable by the test (mosaicism).

DISCLAIMER

- Interpretation of variants in this report is performed to the best knowledge of the laboratory based on the information available at the time of reporting. The classification of variants can change over time and MedGenome cannot be held responsible for this. Please feel free to contact MedGenome Labs (techsupport@medgenome.com) in the future to determine if there have been any changes in the classification of any variations. Re-analysis of variants in previously issued reports in light of new evidence is not routinely performed but may be available upon request.

- Very rarely inspite of having normal report, absence of toxicity cannot be guaranteed because of other rare genetic variations present in *UGT1A1* gene and which are not recommended by PharmGkb.
- The variations have not been validated/confirmed by Sanger sequencing.
- The report shall be generated within agreed turnaround time (TAT), however, such TAT may vary depending upon the complexity of test(s) requested. MedGenome under no circumstances will be liable for any delay beyond afore mentioned TAT.
- It is hereby clarified that the report(s) generated from the test(s) do not provide any diagnosis or opinion or recommends any cure in any manner. MedGenome hereby recommends the patient and/or the guardians of the patients, as the case may be, to take assistance of the clinician or a certified physician or doctor, to interpret the report(s) thus generated. MedGenome hereby disclaims all liability arising in connection with the report(s).
- In a very few cases genetic test may not show the correct results, e.g. because of the quality of the material provided to MedGenome. In case where any test provided by MedGenome fails for unforeseeable or unknown reasons that cannot be influenced by MedGenome in advance, MedGenome shall not be responsible for the incomplete, potentially misleading or even wrong result of any testing if such could not be recognised by MedGenome in advance.
- This is a laboratory developed test and the development and the performance characteristics of this test was determined by MedGenome.

Ram Murthy Anjanappa., PhD

Senior Scientist

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