

Case Report

Reflex Sanger Sequencing Reveals a Rare UGT1A1 *28/*37 Compound Heterozygous Genotype After an Indeterminate Commercial Result in Late-Line Gastric Cancer

Shuhei Suzuki ^{1,*} , Yuka Kobayashi ², Takashi Oizumi ² and Erina Yakuwa ³¹ Department of Clinical Oncology, Yamagata Prefectural Shinjo Hospital, Shinjo 996-8585, Japan² Department of Pharmacology, Yamagata Prefectural Shinjo Hospital, Shinjo 996-8585, Japan³ Department of Nursing, Yamagata Prefectural Shinjo Hospital, Shinjo 996-8585, Japan

* Correspondence: s-suzuki@med.id.yamagata-u.ac.jp; Tel.: +81-(0)233-22-5525; Fax: +81-(0)233-23-2987

Simple Summary

Irinotecan is a chemotherapy drug commonly used for advanced stomach cancer that no longer responds to other treatments. The body relies on a single liver enzyme to clear this drug, and people who inherit certain changes in the gene controlling that enzyme can suffer severe, sometimes fatal, side effects. Standard genetic tests check only the two most common changes. In an older Japanese man, such a test gave an unclear result, so we performed more detailed sequencing of the gene. This revealed an extremely rare combination of two damaging variants, a pattern almost never seen in Japanese people. Because this same combination has previously caused a fatal reaction even at a reduced dose, we chose to avoid the drug entirely rather than simply lower it. Our report shows that an unclear standard test result should prompt confirmatory sequencing rather than a cautious guess, helping make late-line cancer care safer.

Abstract

Background/Objectives: Irinotecan is a key late-line agent in metastatic gastric cancer, but its dose-limiting toxicities—severe neutropenia and diarrhea—are strongly influenced by UGT1A1 promoter polymorphisms. Commercial genotyping kits in Japan routinely interrogate only the common *6 and *28 alleles and may fail to resolve rarer TATA-box variants. We report a case in which an indeterminate commercial result unmasked an extremely rare loss-of-function genotype. **Methods:** A Japanese man in his 60s with HER2-negative, microsatellite-stable metastatic gastric cancer progressing after four prior lines underwent pretreatment UGT1A1 genotyping with a commercial DNA chip in anticipation of irinotecan. When the *28 result returned as indeterminate owing to a TA-ratio error, reflex Sanger sequencing of the UGT1A1 promoter TATA box was performed. **Results:** The chip reported *6 as wild-type but could not resolve *28. Sanger sequencing identified one allele with seven TA repeats (*28) and one with eight TA repeats (*37), with no wild-type six-repeat allele—a *28/*37 compound heterozygote. The *37 allele is exceptionally rare in Japanese individuals (ToMMo 61KJPN allele frequency 0.000294) and has historically been reported almost exclusively in individuals of African ancestry. This genotype has previously caused fatal neutropenic colitis despite preemptive dose reduction. Given the patient's frailty and limited expected benefit, irinotecan was withheld entirely. **Conclusions:** Indeterminate commercial UGT1A1 results may conceal rare loss-of-function alleles with divergent functional consequences. Such results should trigger confirmatory sequencing rather than empiric dose reduction, and institutions should establish reflex pathways in advance to support biomarker-informed, frailty-adapted treatment selection.



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1. Introduction

Advanced gastric cancer that has progressed after fluoropyrimidine, platinum, taxane, and immune checkpoint inhibitor therapy frequently leaves clinicians with few cytotoxic options, and irinotecan remains one of the most commonly employed agents in this late-line setting [1]. Irinotecan is a prodrug that is converted by hepatic carboxylesterases to its active metabolite SN-38, which is subsequently glucuronidated to the inactive SN-38G principally by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Reduced UGT1A1 activity therefore prolongs SN-38 exposure and predisposes patients to severe neutropenia and diarrhea, occasionally with fatal outcomes [2–4]. In Japan, pretreatment UGT1A1 *6 (c.211G>A) and *28 (TA7 promoter repeat) genotyping has become routine practice, and the domestic drug label recommends careful dose consideration in homozygotes and compound heterozygotes of these two alleles [5]. However, the binary “wild-type/variant” output of most commercial kits may obscure rarer variants in the TATA box, including *36 (TA5) and *37 (TA8), the latter of which markedly reduces transcriptional activity and is exceedingly rare in East Asians. We describe a frail patient with late-line gastric cancer in whom a commercial UGT1A1 chip returned an “indeterminate” *28 result, and in whom reflex Sanger sequencing disclosed an extremely rare *28/*37 compound heterozygous genotype, prompting the decision to withhold irinotecan altogether.

2. Materials and Methods

Pretreatment UGT1A1 genotyping was first performed using a commercial DNA chip assay (Gene Silicon DNA Chip Kit UGT1A1, Toyo Kohan, Tokyo, Japan), which interrogates the *6 (c.211G>A) and *28 (TA7 promoter repeat) alleles. Because the *28 result was returned as indeterminate due to a TA-ratio error, reflex confirmatory sequencing was performed. Reflex confirmatory sequencing of the UGT1A1 promoter TATA box was performed as a clinical diagnostic service by an external laboratory (H.U. Frontier Inc., Tokyo, Japan); assay-specific primer sequences and PCR conditions are proprietary to the provider. The resulting electropherogram was compared against the reference sequence [A(TA)₆TAA] to determine the number of TA repeats on each allele.

Population allele frequency data for the UGT1A1*37 (TA8) variant were obtained from the ToMMo 61KJPN reference panel (Tohoku Medical Megabank Organization, Sendai, Japan; <https://jmorp.megabank.tohoku.ac.jp/>, accessed on 2 April 2026), a publicly available whole-genome reference dataset for the Japanese population [6].

3. Case Report

A Japanese man in his 60s, a former factory worker currently unemployed, was referred to our department for further chemotherapy of recurrent gastric cancer. His medical history was notable for insulin-treated type 2 diabetes mellitus, prior glaucoma surgery, and prior coronary surgery for angina pectoris; daily medications consisted of carvedilol, olmesartan, rosuvastatin, a combination of vonoprazan and aspirin, clopidogrel, and amlodipine. He was an ex-smoker with a cumulative exposure of approximately four cigarettes per day for 38 years and reported only occasional alcohol consumption. There was no family history of malignancy or hepatobiliary disease. On examination his chest was unremarkable, an upper abdominal surgical scar was visible, and there was mild bilateral lower extremity edema; the Eastern Cooperative Oncology Group performance status was 1.

In 2021 he had been brought to the emergency department after hematemesis with melena, pallor, and a transient syncopal episode, with an initial hemoglobin of 5.5 g/dL. Emergent esophagogastroduodenoscopy revealed an actively bleeding Borrmann type 2 gastric tumor, which was managed with hemostatic forceps and topical thrombin. Repeat endoscopy on the following day confirmed hemostasis, and biopsy established a diagnosis of advanced gastric adenocarcinoma. The following month, he underwent distal gastrectomy with D1 lymph node dissection and Roux-en-Y reconstruction; pathology demonstrated tub2, pT4N2M0, Stage IIIA disease. Adjuvant chemotherapy was withheld at the patient's preference. Two years later, recurrence manifested as multiple lymph node metastases and peritoneal dissemination, with HER2-negative and microsatellite-stable status. He received first-line S-1 plus oxaliplatin combined with nivolumab [7] and second-line nab-paclitaxel [8], both of which were ultimately discontinued for progressive disease, after which he was referred to medical oncology. On referral his liver function tests, including total bilirubin, were entirely within normal limits (Table 1). Third-line therapy using trifluridine/tipiracil (TAS-102) [9] was initiated, with a clinical response observed.

Table 1. Baseline laboratory data at the time of referral to medical oncology. Total bilirubin and other hepatic function parameters were within normal limits, illustrating the dissociation between routine biochemical screening and underlying UGT1A1 transcriptional capacity.

Biochemistry				Immunology			
		Range				Range	
TP	6.6	6.6–8.1	g/dL	CRP	0.08	0–0.14	mg/dL
Alb	3.8	4.1–5.1	g/dL				
AST	13	13–30	U/L				
						Hematology	
ALT	10	10–42	U/L	WBC	5590	3300–8600	/μL
Total Bil	0.64	0.4–1.3	mg/dL	Hb	10.9	13.7–16.8	g/dL
direct Bil	0.06	0.0–0.2	mg/dL	Plt	192	158–348	×10 ³ /μL
LDH	164	124–222	U/L				
ALP	53	38–113	U/L				
Crea	1.15	0.56–1.07	mg/dL				
UN	18.8	8–20	mg/dL				
Na	141	138–145	mmol/L			Tumor Markers	
K	4.2	3.6–4.8	mmol/L	CEA	26.5	0–5.0	ng/mL
Cl	102	101–108	mmol/L	CA19-9	212	0–37.0	U/mL

CRP: C-reactive protein, CEA: Carcinoembryonic antigen, CA19-9: Cancer Antigen 19-9.

In anticipation of subsequent irinotecan-based therapy, UGT1A1 genotyping was performed using a commercial DNA chip platform (Gene Silicon DNA Chip Kit UGT1A1, Toyo Kohan, Tokyo, Japan). The *6 allele was reported as –/– (wild-type homozygote), but the *28 allele result was returned as “indeterminate” owing to a TA ratio error, which the manufacturer's package insert attributes to an inability to distinguish the canonical TA6/TA7 repeats from a rarer TA5 (*36) or TA8 (*37) allele. Reflex Sanger sequencing of the UGT1A1 promoter TATA box was therefore performed, and definitively identified one allele with seven TA repeats (*28) and the other with eight TA repeats (*37), with no wild-type six-repeat allele present (Figure 1). On detailed pedigree interview, all known ancestors and relatives were of Japanese origin, with no reported African or other non-Asian ancestry. There was no personal history of hyperbilirubinemia or hepatic dysfunction on prior occupational or community health screenings, and no relative had previously undergone UGT1A1 testing because none had been treated with irinotecan. Given the

genotype, irinotecan was withheld from all subsequent treatment plans. Because irinotecan carried a high predicted risk of severe hematologic and gastrointestinal toxicity with only modest expected benefit at this treatment line, it was withheld and was not replaced by an alternative UGT1A1-dependent agent. The patient has continued trifluridine/tipiracil with maintained disease control; at the time of writing, he remains alive and on treatment, and no regimen change has been required. Irinotecan remains held in reserve should later-line options be reconsidered, with the genotype now documented to inform any such decision.

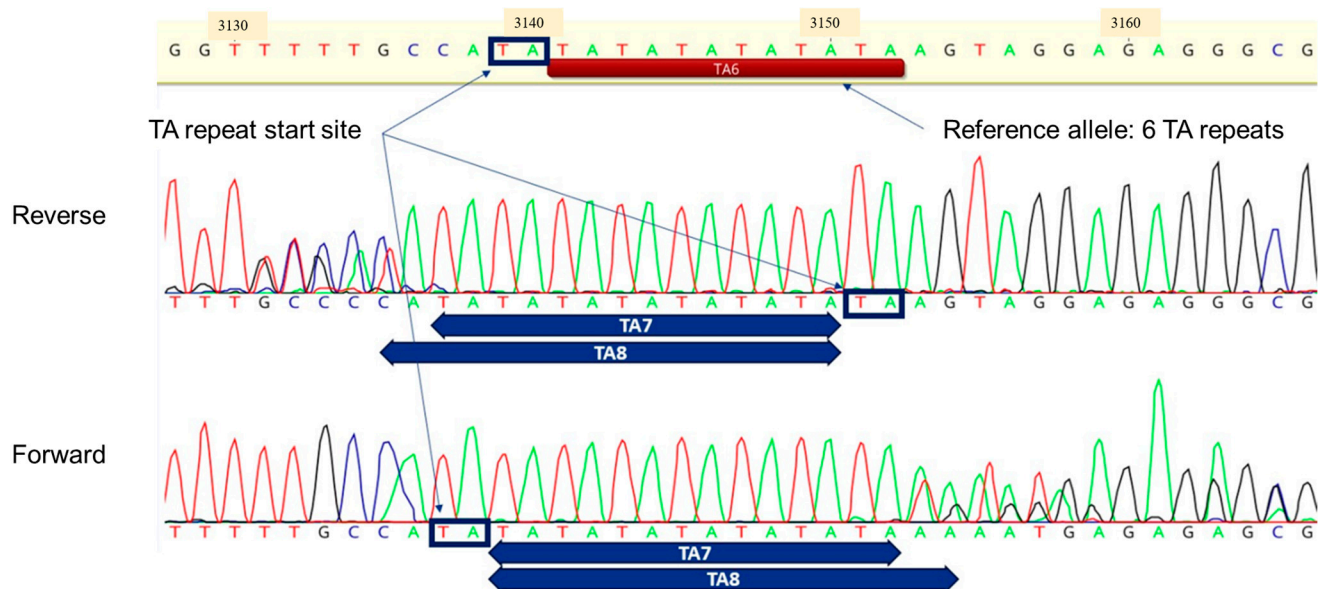


Figure 1. Sanger sequencing electropherogram of the UGT1A1 promoter TATA box. The reference sequence is shown as A(TA)₆TAA. The patient's electropherogram demonstrates superimposed peaks downstream of the TA tract, reflecting a compound heterozygous configuration consisting of one allele with seven TA repeats (*28) and one allele with eight TA repeats (*37), with no wild-type six-repeat allele detectable.

4. Discussion

Beutler and colleagues demonstrated, using a luciferase reporter system in human hepatoma cell lines, that UGT1A1 promoter activity decreases progressively with increasing TA repeat length across the range of five to eight repeats, with TA8 conferring lower transcriptional activity than TA7 [10]. Critically, in their population study of 71 Europeans, 47 Asians, and 101 individuals of African ancestry, TA8-containing alleles were detected exclusively in persons of African ancestry, with an allele frequency of 0.069, and were entirely absent in both European and Asian populations [10]. Our patient—of verified Japanese ancestry with no known African or non-Asian heritage—therefore represents a genotype outside the distribution described in that seminal study.

Irinotecan occupies an unusual position in gastrointestinal oncology. Although it is most firmly established as a backbone agent in colorectal cancer, where FOLFIRI and FOLFIRINOX remain standards of care, it retains a meaningful role in several other malignancies, including as a second- or later-line option in advanced gastric cancer and, in Japan, in gynecologic and lung tumors. Its cytotoxic activity depends on conversion by carboxylesterase to the active metabolite SN-38, a potent topoisomerase I inhibitor, which is then detoxified almost exclusively through UGT1A1-mediated glucuronidation to SN-38G. This narrow, single-enzyme clearance pathway is what makes irinotecan uniquely sensitive to UGT1A1 genotype: when glucuronidation capacity is diminished, SN-38 accumulates and produces the characteristic dose-limiting toxicities of severe neutropenia and delayed-onset diarrhea. Because this pharmacogenetic vulnerability is intrinsic to the drug rather

than to any single tumor type, the testing considerations raised by the present case extend to every setting in which irinotecan is prescribed, not to gastric cancer alone.

The severity implied by this genotype also has a clear molecular basis. UGT1A1 promoter activity is governed by the length of the TATA-box (TA)_n dinucleotide repeat, and transcriptional output falls progressively as the repeat lengthens: the wild-type TA6 supports full expression, TA7 (*28) reduces it, and TA8 (*37) reduces it further still, whereas the shorter TA5 (*36) modestly increases activity. A *28/*37 compound heterozygote therefore carries two loss-of-function promoter alleles of differing but additive severity, yielding a cumulative transcriptional deficit greater than that of the more familiar *28/*28 genotype for which empiric dose reduction was originally calibrated. This distinction matters clinically, because a patient who would already qualify as a poor metabolizer on the basis of *28/*28 may in fact harbor an even more compromised phenotype that standard attenuation was never designed to cover.

The *37 allele is exceptionally uncommon in Japanese populations: according to the ToMMo 61KJPN reference panel (Tohoku Medical Megabank Organization, Sendai, Japan; <https://jmorp.megabank.tohoku.ac.jp/>, accessed on 2 April 2026) [6], the allele frequency of the TA8 variant is 0.000294 (36/122,650), making homozygotes vanishingly rare and *28/*37 compound heterozygotes only marginally less so. To our knowledge, this is the first report of a UGT1A1 *28/*37 compound heterozygous genotype in a Japanese patient, and the first identified in the setting of gastric cancer, with the diagnosis prompted by an indeterminate commercial result and resolved by reflex sequencing. As far as we are aware, clinical descriptions of the *28/*37 genotype in the context of irinotecan therapy are confined to a handful of reports. Most pertinent is the case reported in 2018, in which a patient with metastatic colorectal cancer and a *28/*37 genotype received second-line irinotecan monotherapy at a reduced dose of 150 mg/m², yet developed Grade 4 neutropenia, febrile neutropenia, and fatal neutropenic colitis culminating in septic shock [4]. That outcome, occurring despite preemptive dose attenuation, illustrates that this genotype may not be safely managed by empiric dose reduction alone. Pharmacogenetic guidelines recommend UGT1A1 genotyping before irinotecan and, for poor metabolizers—a category defined by homozygous or compound-heterozygous reduced-function alleles—advise a reduced starting dose rather than avoidance [11]. However, the attenuation validated in clinical and pharmacokinetic studies (a 70% starting dose) derives almost entirely from *28/*28 homozygotes, and no starting dose has been established for the far rarer *28/*37 genotype. We therefore do not suggest that irinotecan is absolutely contraindicated in every *28/*37 carrier; rather, empiric dose reduction may be insufficient, and treatment decisions should be individualized according to genotype, frailty, treatment line, expected benefit, and monitoring capacity.

Several features of the present case deserve emphasis. First, the patient's baseline total bilirubin was unequivocally normal, and he reported no history of hyperbilirubinemia, no familial liver disease, and no non-Japanese ancestry. Each of these features, alone or in combination, might reasonably lead a clinician to assume that no severe UGT1A1 impairment was present. This case demonstrates that the absence of such clinical red flags cannot exclude a profoundly reduced UGT1A1 transcriptional capacity, and that pre-treatment genotyping retains independent predictive value even when the clinical phenotype is unremarkable.

Second, the indeterminate output of the commercial chip-based assay deserves explicit attention. The package insert of the Gene Silicon kit acknowledges that an indeterminate *28 result driven by a TA-ratio error may reflect either a TA5 (*36) or TA8 (*37) allele, because the assay cannot reliably distinguish these from the canonical TA6 and TA7. The *36 allele is a gain-of-function variant typically associated with normal or modestly en-

hanced glucuronidation, whereas *37 is loss-of-function. As noted above, both alleles are vanishingly rare in Japanese populations, and direct clinical experience with the *37 allele remains extremely limited. Because the two candidate alleles carry markedly divergent functional consequences but comparably low prior probabilities, population frequency alone cannot adjudicate an indeterminate result. Reflex Sanger sequencing—or an equivalent confirmatory assay—should therefore be the default response before any irinotecan administration, rather than empiric dose reduction. We propose that institutions offering routine UGT1A1 genotyping establish such a reflex pathway in advance, so that indeterminate results trigger confirmatory sequencing before irinotecan is prescribed rather than ad hoc clinical compromise.

Third, although germline inheritance from one of the patient's parents is the most likely origin of the *37 allele, the rarity of this variant in the local population, combined with the absence of relatives available for segregation analysis, precludes formal confirmation. A *de novo* origin, while improbable, cannot be entirely excluded; functionally, however, this distinction does not alter the immediate therapeutic implication.

Finally, this case illustrates frailty-adapted, biomarker-informed treatment selection in the late-line setting. The patient was frail, had received four prior lines of systemic therapy, and stood to gain only modest incremental benefit from irinotecan even under optimal pharmacogenomic conditions. Against this limited expected benefit, the predicted hepatic and hematologic toxicity arising from a compound loss-of-function UGT1A1 genotype was substantial. Complete withdrawal of irinotecan, rather than empiric dose reduction, was therefore both pharmacologically and ethically defensible. Although a single case cannot establish a generalizable rule, it illustrates a principle we believe is broadly applicable: when an indeterminate UGT1A1 result is encountered in a vulnerable patient, the appropriate response is to confirm the genotype, estimate the cumulative transcriptional deficit, and let that estimate—rather than clinical optimism—guide the treatment decision.

This report has several limitations inherent to a single-patient description. The findings derive from one case and are not statistically generalizable. Because irinotecan was withheld, the clinical consequences of the genotype were inferred from the prior literature rather than observed directly, and no treatment outcome attributable to this genotype can be reported. Finally, the absence of relatives available for segregation analysis precluded formal confirmation of the germline origin of the *37 allele.

5. Conclusions

In a frail patient with heavily pretreated metastatic gastric cancer, an indeterminate commercial UGT1A1 *28 result concealed an extremely rare *28/*37 compound heterozygous genotype resolved only by reflex sequencing. Because this genotype has been associated with fatal toxicity despite preemptive dose reduction, irinotecan was withheld and effective late-line therapy was continued without interruption. Indeterminate UGT1A1 results should prompt confirmatory sequencing rather than empiric dose reduction, and institutions offering routine genotyping should establish a reflex pathway in advance. Decisions in individual carriers should remain individualized according to genotype, frailty, treatment line, expected benefit, and monitoring capacity.

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Informed Consent Statement: Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement: All data relevant to this case are contained within the article. Additional de-identified information is available from the corresponding author upon reasonable request, subject to ethical and privacy restrictions.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

UGT1A1	Uridine diphosphate glucuronosyltransferase 1A1
SN-38	7-Ethyl-10-hydroxycamptothecin (active metabolite of irinotecan)
TA	Thymine–adenine (repeat in the UGT1A1 promoter TATA box)
ToMMo	Tohoku Medical Megabank Organization
61KJPN	61,000 Japanese genomes reference panel (jMorp)
HER2	Human epidermal growth factor receptor 2
ECOG	Eastern Cooperative Oncology Group
S-1	Tegafur/gimeracil/oteracil combination
TAS-102	Trifluridine/tipiracil

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