Distribution of selected gene polymorphisms of UGT1A1 in a Saudi population

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Abstract

Introduction: Glucuronidation is an important phase II pathway responsible for the metabolism of many endogenous substances and drugs to less toxic metabolites, which undergo renal excretion. The aim of the current work was to evaluate genotype and allele frequencies of certain UDP-glucuronosyltransferase 1A1 (UGT1A1) variants in an Arab population.
Material and methods: Genomic DNA was isolated from 192 healthy unrelated Saudi males of various geographic regions and genotyping of UGT1A1*6, *27, *36, *28, *37, and *60 was carried out using polymerase chain reaction (PCR) amplification followed by direct sequencing.
Results: The most common allele for (TA) repeats was the wild type (TA)6 with a frequency of 74.3% followed by the mutant (TA)7 (i.e., UGT1A1*28) with a frequency of 25.7%. The distribution of UGT1A1*60 allele was 62.4% among subjects with the homozygous mutant genotype of 35.4%, while the wild type variant represents 10.6% only. Both UGT1A1*6 and *27 were not detected as all screened subjects showed a homozygous wild type pattern. Similarly, UGT1A1*36* and *37 were either not present or rarely found, respectively. In comparison to other populations, the frequency of UGT1A1*60 and *28 in the studied population was less than that of African Americans but higher than Asians. The geographical origin of the study subjects also implied some differences in genotype distribution of (TA) repeats and UGT1A1*60.
Conclusions: Our data indicate that Saudis harbor some important UGT1A1 mutations known to affect enzyme activity. Additional studies are warranted to assess the clinical implications of these gene polymorphisms in this ethnic group.

Key words: glucuronidation, UDP-glucuronosyltransferase 1A1, gene polymorphism, Saudi Arabians.

Introduction

Glucuronidation catalyzed by UDP-glucuronosyltransferases (UGT) is an important pathway through which endogenous and exogenous

compounds are detoxified to less active counterparts [1]. The UGT1A locus in humans is on the long arm of chromosome 2 (2q37.1) and spans approximately 160 kb. UGT1A contains at least 9 promoters and first exons that can be spliced with four common exons (exons 2–5) to produce UGT1A1-UGT1A9. The UGT2 family is divided into the 2A (three genes) and 2B (seven genes and five pseudogenes) subfamilies on chromosome 4 (4q13). Of the UGT1A isoforms, UGT1A1 (533aa, NM_000463.2) is primarily responsible for the glucuronidation of bilirubin in the human liver and can also conjugate phenols, anthraquinones, flavonoids, and a variety of therapeutic drugs and their metabolites (e.g., SN-38, the active metabolite of irinotecan) [2, 3]. This UGT isoform is expressed in biliary tissue, colon, intestine, liver, and stomach [4].

Alterations in UGT enzyme function may ultimately affect clearance of, and therefore, systemic exposure to those compounds. Several functional polymorphisms in UGT1A1 are associated with reduced bilirubin glucuronidation activity and can cause hyperbilirubinemia (i.e., Gilbert and Crigler-Najjar syndromes). A TA insertion in the UGT1A1 promoter region to produce a (TA)7TAA sequence instead of (TA)6TAA is associated with reduced UGT1A1 transcription [5]. This variant (i.e., (TA)7TAA' UGT1A1*28') is associated with reduced glucuronidation of SN-38 (an active irinotecan metabolite) and bilirubin, as well as the pathogenesis of Gilbert syndrome [6]. Another variant, UGT1A1*60, is a T-to-G substitution at nucleotide –3279 in the UGT1A1 phenobarbital-responsive enhancer module that reduces transcriptional activity [7]. In addition, two single nucleotide polymorphisms (SNPs) are described in exon 1 resulting from G-to-A substitution at 211 nucleotide (Gly71Arg; UGT1A1*6) and C-to-A at 686 nucleotide (Pro229Gln; UGT1A1*27), which are associated with reduced enzyme activity [8, 9].

The prevalence of certain UGT1A variants has been determined in some ethnic groups. The most common non-synonymous SNP (UGT1A1*6) that causes an amino acid alteration (a Gly71Arg switch) is found in Asian populations at frequencies of 13–23% [10]. The UGT1A1*27 genotype has a frequency of 2.8% in Taiwanese [11], while UGT1A1*28/*28 exists in 2.3% of Koreans [12]. The frequency of the UGT1A1*28 homozygous genotype in an Eastern Scottish population was estimated to be 10–13%, whereas the allelic frequency of UGT1A1*60 is 26.2% in Japanese [6, 13].

Apart from a few small sample size reports (n = 42–61) on the frequency of TATA box polymorphism of UGT1A1 in some Middle-Eastern populations [14, 15], information of important UGT1A1 gene variations in the Arabian ethnicity is lacking. Therefore, the aim of this study is to investigate the frequencies of selected UGT1A1 variants in Saudi Arabians and therefore provide essential information on this specific ethnic group. This should also shed some light on the clinical implications of these mutations in relation to disease occurrence and therapeutic efficacy and toxicity of drugs known to be metabolized by UGT1A1.

Material and methods

Human subjects

A total of 192 apparently healthy unrelated Saudi male volunteers (20–25 years old) of various geographic regions were recruited to the study from King Saud University, Riyadh, Saudi Arabia. The study's objectives were explained and one time venous blood sample (~20 ml) was obtained in EDTA tubes from each subject after obtaining written informed consent from all participants. The ethical approval of the study was granted by the Institutional Review Board of the College of Medicine, King Saud University, Riyadh, Saudi Arabia.

Genetic testing

DNA extraction was carried out using Puregene Blood Core Kit C (Qiagen, Germantown, MD, USA) following the manufacturer's instructions and quantified using a Nanodrop 2000 Spectrophotometer (Thermo Scientific, Wilmington, DE, USA). The indicated polymorphic variants were amplified in a Veriti® 96-Well Fast Thermal Cycler (Applied Biosystems, Foster City CA, USA) in a total volume of 25 µl, containing 20 ng DNA, 0.25 µl (2.5 mM) of dNTPs (Epicentre Biotechnologies, Madison, WI, USA), 2 µl (10 pM) of primers (Metabion, Martinsried, Germany) and 0.3 µl (5 U/µl) of HotstarTaq DNA polymerase (Qiagen, Germantown, MD, USA). For PCR, an initial denaturation step at 95°C for 10 min was followed by 35 cycles of denaturation at 94°C for 40 s, annealing at the indicated temperature for 40 s, and extension at 72°C for 45 s, followed by a final extension step of 72°C for 10 min. Primer sequences and their annealing temperatures are listed in Table I. The PCR amplicons were evaluated by 2% agarose gel electrophoresis and then purified using an MCE-membrane MultiScreen plate (Millipore, Billerica, MA, USA) pre-packed with G-50 superfine Sephadex (GE Healthcare, Piscataway, NJ, USA). The purified PCR amplicons were then sequenced by dye termination sequencing using BigDye Terminator Cycle Sequencing V3.1 Kit and 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA, USA). DNA sequences were analyzed using the Seqman program of the DNASTAR analysis package (Lasergene, Madison, WI, USA).

Table I. Primer sequences and annealing temperatures

UGT1A1	Forward primer	Reverse primer	Annealing temperature
UGT1A1*6 (rs4148323)	CAGCAGAGGGGACATGAAAT	CAAAAACATTATGCCCGAGAC	57
UGT1A1*27 (rs35350960)	GGCCTCTCTCCTCTCATTCA	TGGGCCTAGGGTAATCCTTC	57.5
UGT1A1*36,*28,*37 (rs34815109)	TGCTACCTTTGTGGACTGAC	TATCTTCCCAGCATGGGACAC	55
UGT1A1*60 (rs4124874)	ACTTGGTAAGCACGCAATG	GCCTTGCTCTCAAAACTCTG	55

Statistical analysis

Frequency is expressed as percentage with 95% confidence interval (CI). Haplotype frequencies were estimated by the expectation-maximization algorithm (EM algorithm) implemented in PROC Haplotype in SAS Genetics statistical software package (SAS Institute, Cary, NC, USA). The standardized measure of linkage disequilibrium (LD), termed D' and R, was computed at pairs of polymorphic loci.

Results

Allele and genotype frequencies of UGT1A1 are given in Table II. Possible genotypes related to the presence of UGT1A1 variants were observed in the

Table II. Allele and genotype frequencies of UGT1A1 polymorphisms in the Saudi population

Variant	*N*	Frequency [%]	95% CI
Genotype UGT1A1*60 (–3279 T>G)			
UGT1A1*T/*T	20	10.6	(6.2, 14.9)
UGT1A1*G/*G	67	35.4	(28.6, 42.3)
UGT1A1*T/*G	102	54.0	(46.8, 61.1)
Allele			
UGT1A1*T	142	37.6	(32.7, 42.4)
UGT1A1*G	236	62.4	(57.5, 67.3)
Genotype UGT1A1*28,*37 ((TA)6>7,8)			
UGT1A1 *(TA)6/*(TA)6	94	50.0	(43.1, 57.4)
UGT1A1*(TA)6/*(TA)7	90	47.9	(40.9, 55.3)
UGT1A1*TA7/*(TA)7	3	1.6	(0.7, 4.1)
UGT1A1*(TA)8*/*(TA)8	1	0.5	(0.1, 2.4)
Allele			
UGT1A1*(TA)6	278	74.3	(69.9, 78.7)
UGT1A1*(TA)7	96	25.7	(21.2, 30.1)
UGT1A1*(TA)8	2	0.5	(0.2, 1.6)
Genotype UGT1A1*6 (211 G>A)			
UGT1A1*G/*G	182	100	–
UGT1A1*A/*A	0	0	–
UGT1A1*G/*A	0	0	–
Allele			
UGT1A1*G	364	100	–
UGT1A1*A	0	0	–
Genotype UGT1A1*27 (686 C>A)			
UGT1A1*C/*C	181	100	–
UGT1A1*A/*A	0	0	–
UGT1A1*C/*A	0	0	–
Allele			
UGT1A1*C	362	100	–
UGT1A1*A	0	0	–

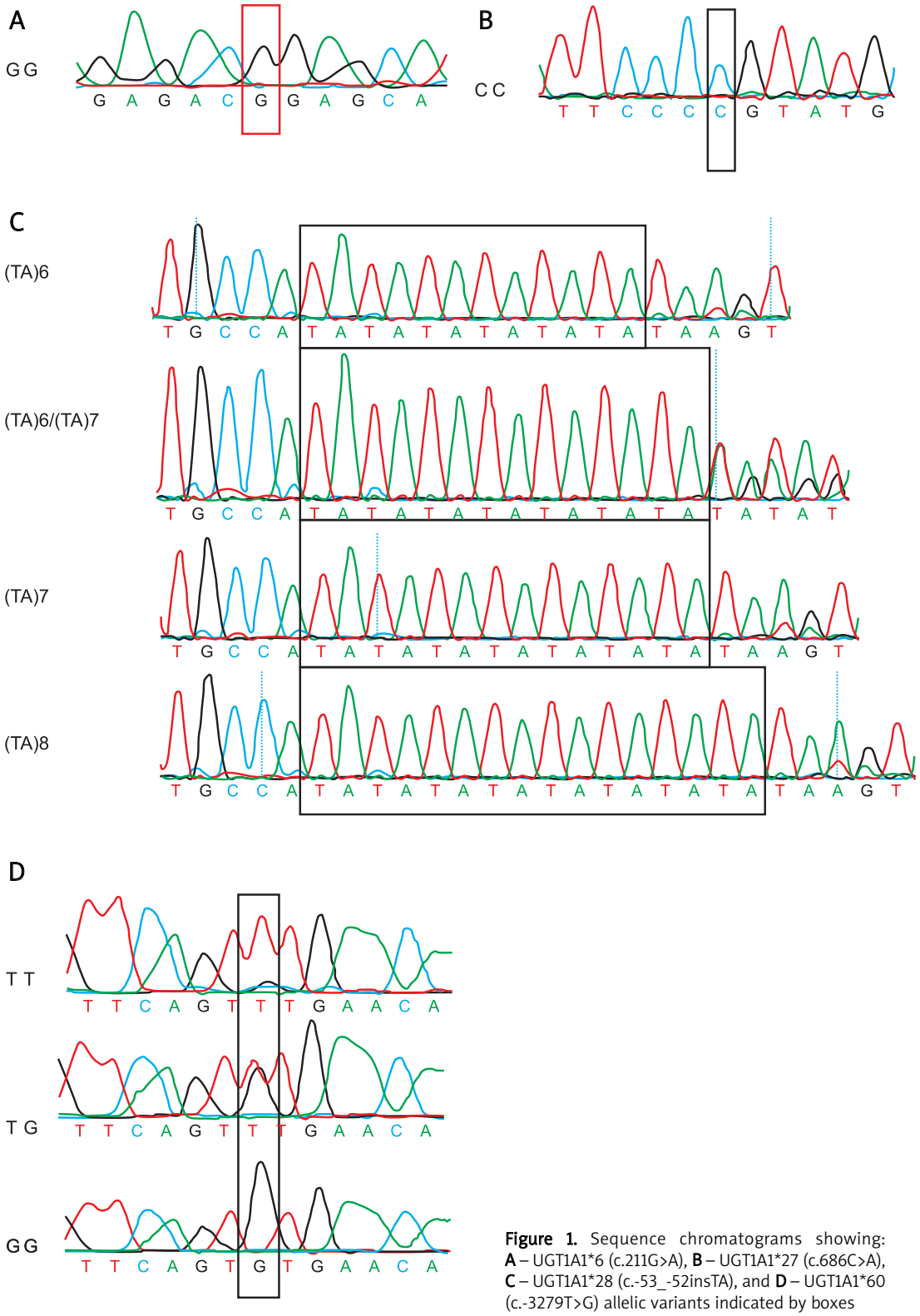

Figure 1. Sequence chromatograms showing: **A** – UGT1A1*6 (c.211G>A), **B** – UGT1A1*27 (c.686C>A), **C** – UGT1A1*28 (c.-53_-52insTA), and **D** – UGT1A1*60 (c.-3279T>G) allelic variants indicated by boxes

studied population. The most common allele for (TA) repeats was (TA)6 with a frequency of 74.3% (n = 278) followed by the mutant (TA)7 allele (i.e., UGT1A1*28) with a frequency of 25.7%. The distribution of UGT1A1*60 allele was 62.4% among subjects with the homozygous mutant genotype of 35.4% (n = 67), while the wild type variant represents 10.6% only. Both UGT1A1*6 and *27 were not detected as all screened subjects showed a homozygous wild type pattern (Figure 1).

Table III. Allele and genotype frequencies of UGT1A1 polymorphisms in Saudi subjects of various geographical origins

Variable	Central (*n* = 80)	Southern (*n* = 52)	Western (*n* = 17)	Northern (*n* = 20)	Eastern (*n* = 32)
UGT1A1*60 (–3279 T>G)					
TT (N)	11	5	3	1	0
GT (N)	39	33	6	11	13
GG (N)	30	13	6	8	10
T (N)	61	43	12	13	0
G (N)	99	59	18	27	33
TT (N% 95% CI)	13.7 (6.2, 21.3)	9.8 (1.6, 17.9)	20 (0.24, 40.2)	5 (1.2, 14.5)	–
GT (N% 95% CI)	48.7 (37.8, 59.7)	64.7 (51.6, 77.8)	40 (15.2, 64.8)	55 (33.2, 76.8)	56.5 (36.3, 76.8)
GG (N% 95% CI)	37.6 (26.8, 48.1)	25.5 (13.5, 37.3)	40 (15.2, 64.8)	40 (18.5, 61.5)	43.5 (23.2, 63.7)
T (N% 95% CI)	38.2 (30.6, 45.6)	42.2 (32.6, 51.7)	40 (22.4, 57.5)	32.5 (17.9, 47.0)	–
G (N% 95% CI)	61.8 (64.3, 69.4)	57.8 (48.3, 67.4)	60 (22.4, 57.5)	67.5 (52.9, 82.0)	100
UGT1A1*TA6,7,8					
UGT1A1*TA6/*TA6 (N)	38	28	9	11	8
UGT1A1*TA6/*TA7 (N)	38	23	7	8	14
UGT1A1*TA7/*TA7 (N)	2	1	0	0	0
UGT1A1*TA8/*TA8 (N)	0	0	1	0	0
UGT1A1*TA6 (N)	114	79	25	30	30
UGT1A1*TA7 (N)	42	25	7	8	14
UGT1A1*TA8 (N)	0	0	2	0	0
UGT1A1*TA6/*TA6 (N% 95% CI)	48.7 (37.6, 59.8)	53.8 (40.3, 67.4)	52.9 (29.2, 76.7)	57.9 (35.7, 80.1)	36.4 (16.2, 56.4)
UGT1A1*TA6/*TA7 (N% 95% CI)	48.7 (37.6, 59.8)	44.2 (30.7, 57.7)	41.2 (29.2, 76.7)	42.1 (19.9, 64.3)	63.6 (43.5, 83.7)
UGT1A1*TA7/*TA7 (N% 95% CI)	2.6 (0.01, 6.1)	2.0 (0.08, 5.6)	–	–	–
UGT1A1*TA8/*TA8 (N% 95% CI)	–		5.9 (2.1, 17.0)	–	–
UGT1A1*TA6 (N% 95% CI)	73.1 (66.1, 80.0)	75.9 (67.7, 84.1)	73.5 (58.7, 88.4)	78.9 (65.9, 91.9)	68.2 (54.4, 81.9)
UGT1A1*TA7 (N% 95% CI)	26.9 (19.9, 33.8)	24.1 (15.8, 32.2)	20.6 (7.0, 34.2)	21.1 (8.1, 34.0)	31.8 (18.1, 45.6)
UGT1A1*TA8 (N% 95% CI)	–	–	5.9 (2.4, 17.4)	–	–
UGT1A1*6 (211 G>A)					
GG (N)	77	46	15	19	23
GG (N% 95% CI)	100	100	100	100	100
UGT1A1*27 (686 C>A)					
CC (N)	74	51	16	19	21
CC (N% 95% CI)	100	100	100	100	100

The geographical origin of participants also revealed some differences in allele distribution. For example, all studied subjects from the Eastern region demonstrated a UGT1A1*60 mutant allele, whereas this mutation was found in about 58–68% in other regions (Table III). Similarly, the UGT1A1*TA6/*TA6 wild genotype was found least often in Eastern Saudis (~36%) and highest in those of Northern descent (~58%). Out of all the studied population, only one subject from the Western

Table IV. UGT1A1 haplotypes in the studied subjects

Haplotype	*N*	Frequency [%]	95% CI
UGT1A1*60G + UGT1A1*(TA)7	30	16.2	(10.9, 21.5)
UGT1A1*60G + UGT1A1*(TA)6	86	46.3	(39.3, 53.7)
UGT1A1*60T + UGT1A1*(TA)7	18	9.5	(5.4, 14.0)
UGT1A1*60T + UGT1A1*(TA)6	51	28.0	(21.1, 34.0)

Table V. Frequencies of UGT1A1 polymorphisms in various populations

Variable	UGT1A1*6	UGT1A1*27	UGT1A1*28	UGT1A1*36	UGT1A1*37	UGT1A1*60	References
Caucasians							
Europeans	ND[a] (50)		0.387 (71)	ND (71)	ND (71)	0.351 (57)	[5, 16–18, 27, 28]
Americans	0.007 (150)	ND (150)	0.388 (147)	0.017 (147)	0.007 (147)	0.550 (150)	
Sardinians			0.257 (70)	ND (70)	ND (70)		
Brazilians			0.324 (71)	0.007 (71)	0.007 (71)		
Africans							
Americans	ND (150)	ND (149)	0.380 (200)	0.080 (200)	0.020 (200)	0.847 (150)	[5, 15, 16, 18, 28, 29]
Brazilians			0.407 (54)	0.065 (54)	0.009 (54)		
Kenyans			0.444 (80)	0.100 (80)	0.013 (80)		
Asians							
Japanese	0.153 (301)	0.003 (149)	0.130 (301)	ND (301)	ND (301)	0.262 (301)	[13, 18, 24, 25, 30]
Koreans	0.213 (324)		0.127 (324)	ND (324)	ND (324)	0.267 (324)	
Chinese	0.230 (50)		0.160 (89)	ND (89)	ND (89)	0.300 (50)	
Indians	0.032 (94)		0.408 (119)	ND (119)	ND (119)	0.871 (176)	
Middle-Easterners							
Yemenite			0.254 (61)	ND (61)	ND (61)		[14, 15]
Lebanese			0.357 (42)	ND (42)	ND (42)		
Egyptians			0.260 (50)				
Saudis[b]	ND (184)	ND (182)	0.257 (191)	ND (191)	0.005 (191)	0.624 (191)	

[a]*ND – not detected,* [b]*The current study*

region carries the (TA)8 repeats variant (i.e., UGT1A1*37); the (TA)5 repeats variant (i.e., UGT1A1*36) was not present in the studied population. Table IV represents UGT1A1 haplotypes identified in our study. UGT1A1*60 allele was found to be in a combination with UGT1A1*28 allele in about 16.2% of subjects, while with UGT1A1 (TA)6 allele in 46.3% (95% CI: 39.3, 53.7). The linkage disequilibrium D' between UGT1A1*60 and UGT1A1*28 was estimated to be 0.003 with a correlation coefficient (R^2) of 0.005 (p = 0.95), concluding no association between the two loci from the studied population.

Discussion

To our knowledge, the current study is the first to indicate the distribution of some UGT1A1 in Saudi Arabians. The frequency of UGT1A1*60 in the studied population is less than African Americans and Asian Indians but more than that of Chinese and Japanese. On the other hand, UGT1A1*28 prevalence in Saudis is comparable to Egyptians and Yemenites, whereas it is 2-fold higher than Koreans [12, 14]. Similar to other populations, UGT1A1*37 is a rare mutation [16–18]. The frequencies of these repeat polymorphisms in various populations are given in Table V.

In vitro and *in vivo* studies showed that increasing the TA repeat number leads to a decrease in the transcriptional activity of UGT1A1. Given the transcriptional activity of n = 6 defined as 100%, those of n = 5, 7, and 8 were approximately 130%, 65% and 50%, respectively [5]. Patients who are homozygous for the UGT1A1*28 allele may develop severe, dose-limiting toxicity (diarrhea, neutropenia) dur-

ing irinotecan therapy [19] and a mild type of inherited Gilbert's syndrome [6, 20]. Therefore, a dosing scheme based on the presence of a UGT1A1*28 genotype is currently recommended [21].

Another 1A1 polymorphism 211G>A (G71R, *6 allele) in exon 1 is also a causative factor for Gilbert's syndrome [22], reduced metabolic activity to SN-38 [23], and lower tumor response and higher incidence of grade 4 neutropenia in Koreans [24]. In the current study, we did not detect UGT1A1*6 polymorphism in Saudis. In addition, 1A1*60 allele (–3279T>G) is located in the distal enhancer region, a phenobarbital-responsive enhancer module, and shows reduced transcriptional activity [7]. This polymorphism was found to be about 2-3-fold more prevalent among studied Saudis compared to Oriental Asians [25]. The combination of UGT1A1*60 allele and UGT1A1*28 allele in about 16.2% of Saudis may represent a risk of reduced enzyme activity, despite the low D' value. Therefore, the clinical implication of such variants in relation to irinotecan therapy should be further explored in Saudi patients. A minor allele, UGT1A1*27, which has been reported to be associated with Gilbert's syndrome and possibly grade 4 neutropenia with irinotecan-based chemotherapy in Asians [22, 26], was not detected in the current study. One limitation of the current study is the lack of gender effect as all screened subjects were males. This however is expected have a minimal consequence for the findings as no sexual dimorphism was previously reported for the human UGT1A1 locus.

In conclusion, the frequencies of important UGT1A1 variants (i.e., UGT1A1*6, UGT1A1*27, UGT1A1*28, UGT1A1*36, UGT1A1*37, and UGT1A1*60) were determined in Saudi Arabians. Both UGT1A1*60 and *28 prevalence is less than in those of African origin but higher than those of Oriental descent. Other studied mutations were either not present or rarely detected. Further studies are needed to investigate the phenotypic patterns of UGT1A1 genotypes in the Arab population.

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