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REVIEW ARTICLE

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Bilirubin metabolism and UDP-glucuronosyltransferase *1A1* variants in Asians: Pathogenic implications and therapeutic response

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Abstract

In the Asian general population, at least six single-nucleotide variants (SNVs) in the UDP-glucuronosyltransferase (UGT) *1A1* gene have been identified: −3279T>G, −53A(TA)$_6$TAA>A(TA)$_7$TAA, 211G>A, 686C>A, 1091C>T, and 1456T>G. Each of these six SNVs was observed in at least four ethnic groups of the 12 Asian populations studied. In East Asian populations, the descending frequency of these six SNVs was as follows: −3279G>[−53A(TA)$_7$TAA, 211A]>(686A, 1091T)>1456G. Because of the presence of linkage disequilibrium and the expulsion phenomenon, when the SNVs −3279G, −53A(TA)$_7$TAA, 211A, and 686A were simultaneously involved, 15 instead of the estimated 81 genotypes were observed. Those carrying 686AA or 1456GG developed Gilbert's syndrome or Crigler–Najjar syndrome type 2. Both −53A(TA)$_7$TAA/A(TA)$_7$TAA and 211AA are the main causes of Gilbert's syndrome in East Asian populations. In East Asian populations, the 211AA genotype is the main cause of neonatal hyperbilirubinemia, whereas −53A(TA)$_7$TAA/A(TA)$_7$TAA exerts a protective effect on hyperbilirubinemia development in neonates fed with breast milk. Both 211A and −53A(TA)$_7$TAA are significantly associated with adverse drug reactions induced by irinotecan (one of the most widely used anticancer agents) in Asians. However, at least three common SNVs (−3279G, −53A(TA)$_7$TAA, and 211A) should be comprehensively analyzed. This study investigated the clinical significance of these six SNVs and demonstrated that examining *UGT1A1* variants in Asian populations is considerably challenging.

KEYWORDS

adverse drug reaction, Gilbert's syndrome, neonatal hyperbilirubinemia, single-nucleotide variants, UDP-glucuronosyltransferase *1A1* gene

1 | INTRODUCTION

UDP-glucuronosyltransferase 1A1 (UGT1A1), the sole enzyme responsible for the glucuronidation of bilirubin in humans, is encoded by the *UGT1A1* gene located on chromosome 2q37.1.[1] Bilirubin, the end product of heme catabolism, is primarily obtained through the breakdown of erythrocyte hemoglobin, and it is poorly soluble in water. As illustrated in Figure 1, unconjugated bilirubin is transported by organic anion transport protein 2 (OATP2) to the smooth endoplasmic reticulum of hepatocytes, where the conjugating enzyme

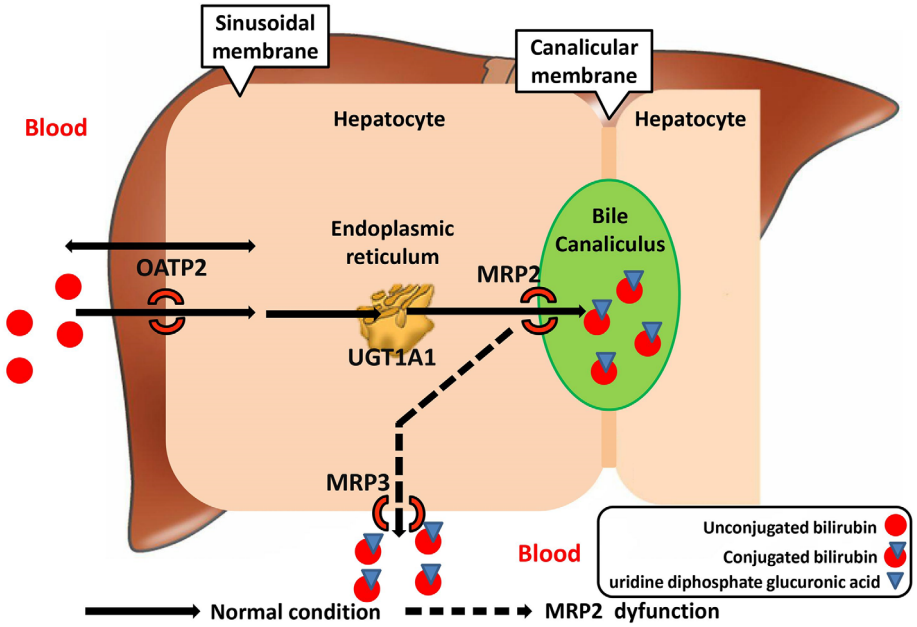

FIGURE 1 Mechanism of bilirubin elimination.

TABLE 1 MAF for every SNVs of the *UGT1A1* gene

	−3279T>G	−536>7	211G>A	686C>A	1091C>T	1456T>G
East Asia						
Chinese[6–8]	0.320	0.118	0.185	0.014	0.021	0.003
Chinese Tibetan[9]	N/A[a]	0.130	0.200	0	0.085	0
Japanese[10]	0.262	0.130	0.153	0.010	0.005	0.002
Korean[11,12]	0.267	0.200	0.173	0.014	0.013	0.001
Taiwanese[3,13]	0.350	0.143	0.109	0.028	0.021	0.002
Southern-East Asia						
Indonesian[14]	N/A	0.095	0.048	0.030	0	0
Malaysian Malay[15]	N/A	0.250	0.120	0.030	N/A	N/A
South East Asian Malay[16]	0.432	N/A	0.057	0.031	0.010	N/A
Thai[17]	0.286	0.051	0.027	N/A	N/A	N/A
Vietnamese[18]	N/A	0.060	0.050	0	N/A	N/A
Southern Asia						
Indian[19]	0.431	0.336	0.066	0	0	0
Central Asia						
Uzbek[20]	0.500	0.310	0.090	0.005	N/A	N/A
West Asia						
Saudi[21]	0.624	0.262	0	0	N/A	N/A

Abbreviations: MAF, minor allele frequency; SNV, single-nucleotide variant; UGT, UDP-glucuronosyltransferase; 6 > 7, $A(TA)_6TAA>A(TA)_7TAA$.
[a]Not assayed.

UGT1A1 is localized. Subsequently, unconjugated bilirubin is conjugated with uridine diphosphate glucuronic acid to form mono- and di-glucuronide bilirubin (water soluble); this reaction is catalyzed by UGT1A1.[1,2] At the canalicular surface, conjugated bilirubin is efficiently secreted into bile through the ATP-binding cassette (ABC) multidrug resistance–associated protein (ABCC2/MRP2) transporter. The excretion of conjugated bilirubin at the basolateral surface is mediated by the transporter ABCC3/MRP3.[1,2]

Altered and variant *UGT1A1* genes can cause fatal or benign types of unconjugated hyperbilirubinemia, namely Crigler–Najjar syndrome type 1 (CN-1), Crigler–Najjar syndrome type 2 (CN-2), and Gilbert's syndrome (GS).[1,2] Moreover, the association of *UGT1A1* with the metabolic rate of certain drugs or the risk of cancer has been reported.[2] Therefore, the single-nucleotide variants (SNVs) of *UGT1A1* represent crucial changes to the gene structure.

The cDNA of human *UGT1* was cloned in 1991.[1] Genetic defects in *UGT1A1* that cause CN-1, CN-2, and GS were first reported in 1992, 1993, and 1995, respectively.[1,2] Thereafter, many studies have identified genetic defects in *UGT1A1* in different populations. In the Asian general population, at least six SNVs of *UGT1A1* have been reported[1,3–5]: −3279T>G, −53A(TA)$_6$TAA>A(TA)$_7$TAA, 211G>A, 686C>A, 1091C>T, and 1456T>G. Table 1 summarizes the distributions of these six SNVs. The SNVs 211G>A, 686C>A, 1091C>T, and 1456T>G have been observed in Asians, but never in Caucasians.

We searched for studies examining genetic defects in *UGT1A1* in healthy Asians, patients with GS, and neonates with nonhemolytic unconjugated hyperbilirubinemia that were indexed in PubMed since 1995 and included those in this review. We excluded case reports and review articles. To examine the association among the six SNVs, studies focusing on at least three of the six SNVs were included. A total of 66 studies published until December 31, 2021, met the inclusion criteria and were included in this review. Of the 66 studies, 20 included Chinese populations[5–9,22–36] (two studies also included Chinese Tibetan individuals[9,22]), 4 included Indian populations,[19,37–39] 2 included Indonesian populations,[14,40] 12 included Japanese populations[4,10,20,41–49] (one study also included individuals from Uzbekistan[20]), 4 included Korean populations,[11,12,50,51] 3 included Malaysian populations,[15,16,52] 1 included Saudi individuals,[21] 18 included Taiwanese individuals,[1,3,13,53–67] 1 included Thai individuals,[17] and 1 included Vietnamese individuals.[18] Moreover, we reviewed all the studies examining the relationship between the variants of *UGT1A1* and the adverse drug reaction (ADR) or therapeutic efficacy of irinotecan-based chemotherapy in Asian patients with colon cancer published in PubMed from 2018 to 2021.

We conducted a comprehensive analysis of *UGT1A1* variants in the Asian populations.

2 | ALLELE FREQUENCIES AND UGT1A1 ENZYME ACTIVITIES OF THE SIX SNVS

2.1 | Allele frequencies

In this review, the minor allele frequency (MAF) of an SNV was collected from healthy adults' data. However, because of the unavailability of data for healthy adults in the Indonesian and Vietnamese populations, we used data obtained from newborns without hyperbilirubinemia for these two ethnic groups. If the MAF of an SNV in an ethnic group was reported in two (or more) studies, the study with a larger sample size was selected as the example for that ethnic group.

Table 1 presents the MAFs of the six SNVs reported for 12 populations: Chinese,[6–8] Chinese Tibetan,[9] Japanese,[10] Korean,[11,12] Taiwanese,[3,13] Indonesian,[14] Malaysian,[15,16] Thai,[17] Vietnamese,[18] Indian,[19] Uzbek,[20] and Saudi.[21] Each of the six SNVs was observed in at least four ethnic groups. The MAF of −3279T>G was higher than 0.430 in the Malaysian, Indian, Uzbek, and Saudi populations (0.431–0.624) but was ≤0.350 in the Chinese, Japanese, Korean, Taiwanese, and Thai populations (0.262–0.350). The MAF of −53 A(TA)$_6$TAA>A(TA)$_7$TAA was ≥0.250 in the Malaysian, Indian, Uzbek, and Saudi populations (0.250–0.336); between 0.118 and 0.200 in the Chinese, Chinese Tibetan, Japanese, Korean, and Taiwanese populations; and as low as 0.095, 0.051, and 0.060 in the Indonesian, Thai, and Vietnamese populations, respectively. The MAF of 211G>A was ≤0.090 in the Indonesian, Malaysian, Thai, Vietnamese, Indian, Uzbek, and Saudi populations (0–0.090) but ≥0.109 in the other five ethnic groups (0.109–0.200). The MAF of 686C>A was ≥0.028 in the Taiwanese, Indonesian, and Malaysian populations (0.028–0.031); between 0.010 and 0.014 in the Chinese, Japanese, and Korean populations; and ≤0.005 in the Chinese Tibetan, Vietnamese, Indian, Uzbek, and Saudi populations (0–0.005). The MAF of 1091C>T was as high as 0.085 in the Chinese Tibetan population; between 0.010 and 0.021 in the Chinese, Korean, Taiwanese, and Malaysian populations; and ≤0.005 in the Japanese, Indonesian, and Indian populations (0–0.005). The MAF of 1456T>G was considerably low in the Chinese, Chinese Tibetan, Japanese, Korean, Taiwanese, Indonesian, and Indian populations (0–0.003). The results indicated that the MAFs of the promoter region were higher in the West Asian, Central Asian, and Southern Asian populations than in the East Asian populations, whereas the MAFs of the coding region were higher in the East Asian populations than in the West Asian, Central Asian, and Southern Asian populations.

The geographical origin of the study participants may be responsible for some differences in the genotype distribution of *UGT1A1*. All the six SNVs observed in the Chinese, Japanese, Korean, and Taiwanese populations were characterized by the descending MAF order of −3279G>[−53A(TA)$_7$TAA, 211A]>(686A, 1091T)>1456G.

2.2 | UGT1A1 enzyme activities

The SNVs of *UGT1A1* in the promoter area affect the transcription of the enzyme, and those within the coding region cause a change in its expression. UGT1A1 activities for −3279GG, −53A(TA)$_7$TAA/A(TA)$_7$TAA, 211AA, 211GA, 686AA, 1091TT, and 1456GG are listed in Table 2. Those data were obtained from experiments performed to examine the protein expression of cDNAs in COS-7 monkey kidney cells, except for −53A(TA)$_7$TAA/A(TA)$_7$TAA that was detected in the human hepatoma cell line (HuH7).[1] The UGT1A1 enzyme activity of the 211GA SNV was estimated ([32.2% (activity for 211AA)]$^{1/2}$) to be 56.7% of normal, which is close to 60.2% of normal for the determined activity.[1] Therefore, the estimated UGT1A1 activities for the heterozygote [(activity for the homozygote)$^{1/2}$] of the SNVs −3279T>G, −53A(TA)$_6$TAA>A(TA)$_7$TAA, 686C>A, 1091C>T, and 1456T>G (Table 2) appear to be reasonable.[1]

3 | LINKAGE DISEQUILIBRIUM, EXPULSION PHENOMENON, AND OBSERVED AND NEVER-OBSERVED GENOTYPES

3.1 | Linkage disequilibrium

Several studies examining the linkage disequilibrium of the SNVs of *UGT1A1* have been published since 2002.[68] In this review,

TABLE 2 Characteristics of the six SNVs in the *UGT1A1* gene

	−3279T>G	−536>7	211G>A	686C>A	1091C>T	1456T>G
Location	Promoter	Promoter	Exon 1	Exon 1	Exon 4	Exon 5
Amino acid	No change	No change	Gly71Arg	Pro229Gln	Pro364Leu	Tyr486Asp
Allele name	UGT1A1*60	UGT1A1*28	UGT1A1*6	UGT1A1*27	UGT1A1*63	UGT1A1*7
Rs number	4124874	8175347	4148323	35350960	34946978	34993780
Activity, % of normal	TG, 77.5[a] GG, 60.0[b]	6/7, 50.5[a] 7/7, 25.5[c]	GA, 60.2[b] AA, 32.2[b]	CA, 37.4[a] AA, 14.0[b]	CT, 59.7[a] TT, 35.6[b]	TG, 27.6[a] GG, 7.6[b]

Abbreviations: SNV, single-nucleotide variant; UGT, UDP-glucuronosyltransferase; 6 > 7, A(TA)$_6$TAA>A(TA)$_7$TAA; 7/7, A(TA)$_7$TAA/A(TA)$_7$TAA.
[a]Estimated value, by calculation [(activity for the homozygote)$^{1/2}$].
[b]Detected in COS-7 monkey kidney cells.
[c]Detected in the human hepatoma cell line (HuH7).

we observed that the 686 CA genotype was associated with the −53A(TA)$_6$TAA/A(TA)$_7$TAA or −53A(TA)$_7$TAA/A(TA)$_7$TAA SNV.[1,10,30,54–56,58,59,66,67] When −3279T>G was considered, 686CA was observed to be closely associated with not only −53A(TA)$_6$TAA/A(TA)$_7$TAA or −53A(TA)$_7$TAA/A(TA)$_7$TAA but also −3279TG or −3279GG.[1,66] The 686AA genotype was associated with the −53A(TA)$_7$TAA/A(TA)$_7$TAA SNV,[1,56,58] and −53A(TA)$_7$TAA/A(TA)$_7$TAA was associated with −3279GG.[1,3,66,68] However, −53A(TA)$_6$TAA>A(TA)$_7$TAA was not associated with 686C>A,[1,10,30,54–56,58,59,66,67] and −3279T>G was not associated with −53A(TA)$_6$TAA>A(TA)$_7$TAA.[1,3,34,66,69] In these relationships, the degree of linkage disequilibrium (D') was high, whereas r^2 was low for the association between −3279G and −53A(TA)$_7$TAA ($D' = 0.95$, $r^2 = 0.26$) and between −53A(TA)$_7$TAA and 686A ($D' = 0.95$, $r^2 = 0.13$).[66] A high D' but a considerably low r^2 value was noted for the association between 686A and −3279G ($D' = 0.95$, $r^2 = 0.03$).[66]

3.2 | Expulsion phenomenon

All the studies examining the SNVs 211G>A, −3279T>G, −53A(TA)$_6$TAA>A(TA)$_7$TAA, and 686C>A reported that individuals possessing 211AA never carried −3279TG, −3279GG, −53A(TA)$_6$TAA/A(TA)$_7$TAA, −53A(TA)$_7$TAA/A(TA)$_7$TAA, 686CA, or 686AA. Those possessing 211GA never carried −3279GG, −53A(TA)$_7$TAA/A(TA)$_7$TAA, or 686AA. Therefore, the expulsion phenomenon was observed between 211AA and −3279G, between 211AA and −53A(TA)$_7$TAA, and between 211AA and 686A. In addition, the expulsion phenomenon was observed between 211GA and −3279GG, between 211GA and −53A(TA)$_7$TAA/A(TA)$_7$TAA, and between 211GA and 686AA. Such expulsion phenomenon may spontaneously occur in meiosis during the homologous recombination process after fertilization.

3.3 | Observed and never-observed genotypes

Among the six SNVs, −3279G, −53A(TA)$_7$TAA, and 211A were commonly observed because the MAFs of all the three SNVs were ≥0.05, except for in the Indonesian,[14] Thai,[17] and Saudi populations[21] with

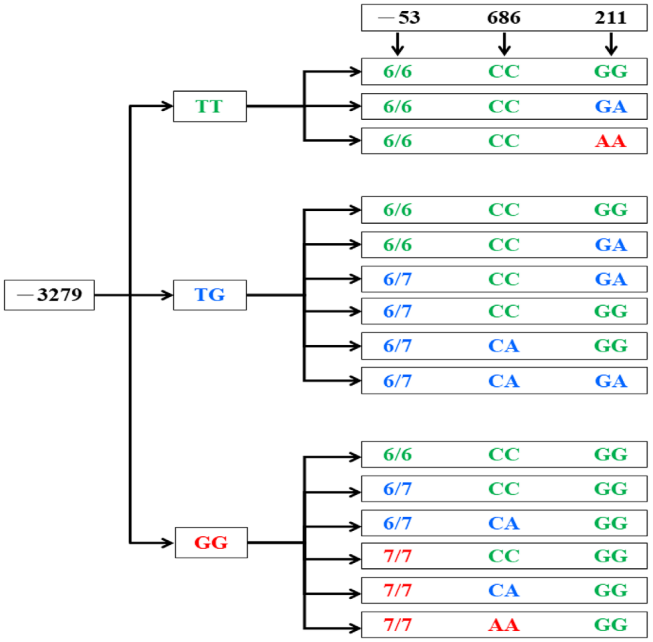

FIGURE 2 The 15 observed genotypes (combination of the four SNVs at nucleotides −3279, −53, 686, and 211 in *UGT1A1*) [green color: Wild type, blue color: Heterozygote, red color: Homozygote; 6/6, A(TA)$_6$TAA/A(TA)$_6$TAA; 6/7, A(TA)$_6$TAA/A(TA)$_7$TAA; 7/7, A(TA)$_7$TAA/A(TA)$_7$TAA].

MAFs of 0.048, 0.027, and 0 for 211A, respectively (Table 1). Linkage disequilibrium was observed in the SNVs −3279G, −53A(TA)$_7$TAA, and 686A. Therefore, the four SNVs at nucleotides −3279, −53, 686, and 211 in *UGT1A1* were combined for further analysis. When the three SNVs at nucleotides −53, 686, and 211 were combined, the estimated number of genotypes was 27 (3^3). However, for those carrying −3279TT, −3279TG, and −3279GG, only three, six, and six genotypes of the SNVs for combined nucleotides (−53/686/211) were noted, respectively (Figure 2). Therefore, among the estimated 81 (3^4) genotypes for the combination of the four SNVs at nucleotides −3279, −53, 686, and 211, a total of 15 genotypes were observed, whereas the other 66 genotypes were never observed (Table 3).

Figure 2 presents the distribution of the 15 observed genotypes. The results revealed that the wild type of nucleotide −3279 could

TABLE 3 Estimated, observed and never-observed genotypes by combination of four SNVs at nucleotides 686, −53, −3279, and 211 in the *UGT1A1* gene

	Combined SNVs at nucleotides	N estimated genotypes	Genotypes observed	Genotypes never observed
686AA	−53, −3279, and 211	27	−53(7/7)/−3279GG/211GG	Other 26 estimated-genotypes
686CA	−53, −3279, and 211	27	−53(6/7)/−3279TG/211GG, −53(6/7)/−3279TG/211GA, −53(6/7)/−3279GG/211GG, −53(7/7)/−3279GG/211GG	Other 23 estimated-genotypes
686CC/−53(7/7)	−3279 and 211	9	−3279GG/211GG	Other eight estimated-genotypes
686CC/−53(6/7)	−3279 and 211	9	−3279TG/211GG, −3279TG/211GA, −3279GG/211GG	Other six estimated-genotypes
686CC/−53(6/6)	−3279 and 211	9	−3279TT/211GG, −3279TT/211GA, −3279TT/211AA, −3279TG/211GG, −3279TG/211GA, −3279GG/211GG	−3279TG/211AA, −3279GG/211AA, −3279GG/211GA

Abbreviations: SNV, single-nucleotide variant; UGT, UDP-glucuronosyltransferase; 6/6, $A(TA)_6TAA/A(TA)_6TAA$; 6/7, $A(TA)_6TAA/A(TA)_7TAA$; 7/7, $A(TA)_7TAA/A(TA)_7TAA$.

predict the presence of the wild-type gene at nucleotide −53 is, and the wild type of nucleotide −53 could predict the presence of the wild-type gene at nucleotide 686. By contrast, the wild type of nucleotide 686 (CC) could not predict whether nucleotide −53 is wild type [$A(TA)_6TAA/A(TA)_6TAA$], and the wild type of nucleotide −53 could not predict whether nucleotide −3279 is wild type (TT). Furthermore, the homozygote of −3279 (GG) predicted that nucleotide 211 is wild type (GG). Therefore, to determine the four SNVs, the SNV of −3279 should be first identified, followed by the SNVs of −53, 686, and 211.

4 | VARIATION STATUS OF *UGT1A1* AND DISEASES

4.1 | Crigler–Najjar syndromes

The UGT1A1 enzyme activity was 0% and approximately 10% of normal in patients with CN-1 and CN-2, respectively.[1] The corresponding serum bilirubin levels ranged from 342 to 855 μmol/L in patients with CN-1 and from 103 to 342 μmol/L in those with CN-2.[1] In CN-1, common mutations are deletions, alterations in intron splice donor and receptor sites, missense mutations, exon skipping, insertion, and stop codon formation within *UGT1A1*. By contrast, CN-2 results from a point mutation in *UGT1A1*.[2,5,33,46,70] In Caucasian patients with CN-2, point mutations were widely distributed and often combined with $-53A(TA)_6TAA/A(TA)_7TAA$ or $-53A(TA)_7TAA/A(TA)_7TAA$, whereas compound homozygous variations in the coding region were frequently observed in Asian patients with CN-2.[70] Among 27 East Asian patients with CN-2, 14 (51.8%) were carriers of 1456GG/211AA.[70] For the carriers of 1456GG/211AA, UGT1A1 activity was approximately 6% of normal.[71] The findings indicate that 1456GG/211AA causes CN-2. Moreover, 1456GG/211GA, 1091TT/211GA, and 1091TT/−3279GG were observed in Asian patients with CN-2.[31,70] The 1456G and 1091T have never been reported in patients of other ethnicities expect East Asian patients, whereas 1091C>T was observed in South East Asian Malaysians (Table 2). The results indicate that for the development of CN-2, the variation status of *UGT1A1* differs between Asians and Caucasians and between East Asians and other Asian ethnic groups.

4.2 | Glibert's syndrome

In patients with GS, the UGT1A1 enzyme activity ranges from 11% to approximately 30% of normal, and the serum bilirubin level ranges from 17 to 103 μmol/L.[1] Although 9%–18% of healthy Caucasians harbored the $-53A(TA)_7TAA/A(TA)_7TAA$ genotype, this genotype is the main genetic cause of GS in Caucasians.[1,2] However, we observed that both $-53A(TA)_7TAA/A(TA)_7TAA$ and 211AA are the main genetic causes of GS in Asians, except in the Indian,[19,39] Malaysian,[16] and Saudi[21] populations because the 211G>A variation did not affect unconjugated bilirubin levels in these three ethnic groups. Our finding is in agreement with previously reported data.[72] In addition, we observed that individuals carrying $-53A(TA)_7TAA/A(TA)_7TAA$ or 211AA had a high risk of GS because only 0%–2.8% of healthy Asians harbored these two variants. UGT1A1 activity in patients carrying 686AA was 14.0% of normal.[1] The finding indicates that 686AA causes GS. For the development of GS, the variation status of *UGT1A1* differs between Asians and Caucasians.

Recently, a study conducted in Taiwan determined the six SNVs of *UGT1A1* and reported that an UGT1A1 activity of ≤40% of normal is a risk factor for GS.[1] The authors concluded that evaluating UGT1A1 activity rather than analyzing the SNVs and genotypes of *UGT1A1* should provide more information regarding the mechanisms underlying the development of GS.[1]

In Asian populations, the variants of UGT1A1 combined with OATP2,[7,39,58] glucose-6-phosphate dehydrogenase (G6PD),[56,58] heme oxygenase 1 (HMOX1-1),[39] and biliverdin reductase A (BLVRA)[39]

exert additive effects on adult patients with mild unconjugated hyperbilirubinemia. However, mildly elevated unconjugated bilirubin in GS is strongly associated with a decreased prevalence of chronic diseases, particularly cardiovascular diseases and type 2 diabetes mellitus, as well as cardiovascular disease-related and all-cause mortality.[72]

4.3 | Neonatal hyperbilirubinemia

The main genetic cause of neonatal hyperbilirubinemia is −53A $(TA)_7$TAA/A$(TA)_7$TAA in Caucasians,[73] whereas 211AA, but not −53A $(TA)_7$TAA/A$(TA)_7$TAA, is the main genetic cause in Asians.[73,74] The results of our review confirmed these findings (except for Indonesian,[14,40] Malaysian,[52] and Saudi[21] populations). Moreover, the TA_7 repeat variant of *UGT1A1* appears to exert a protective effect on hyperbilirubinemia development in Chinese,[28] Japanese,[48,75] and Taiwanese[57,67] neonates fed breast milk. Breast milk suppresses UGT1A1 expression in the small intestine, and this undefined environmental pressure induces the (TA)n repeat to maintain serum bilirubin levels. The (TA)n repeat might be a balanced variation evolutionarily selected to maintain serum bilirubin in an optimal range under undefined genetic and environmental pressure.[67,76] The results of a study conducted in Taiwan demonstrated that the estimated enzyme activity, depending on the combination of *UGT1A1* genotypes cannot be used to explain the development of neonatal hyperbilirubinemia because the expression of UGT1A1 in neonates remains unclear.[67]

In Asians, G6PD deficiency,[54,61,65] variations in *OATP2*,[26,57,76] variations in *HMOX1-1*,[65,76] variations in *BLVRA*,[76] and ABO incompatibility hemolysis disease[35] are additive risk factors for neonatal hyperbilirubinemia in newborns carrying homozygous 211G to A variation in *UGT1A1*.

4.4 | Further concern for variations on common exons

Four exons (exons 2–5) are common in the nine functional UGT1A alternatively spliced products transcribed from the UGT1A gene locus, namely UGT1A1 and UGT1A3–UGT1A10.[9] A common exon variation in *UGT1A1* affects the activities of all functional UGT1As. Among the six SNVs analyzed in this study, the 1091C>T (p.Pro364Leu) and 1456T>G (p.Tyr486Asp) are crucial because they are located on exons 4 and 5, respectively. These two variations are located close to the UDP-glucuronic acid binding site and lead to considerable reduction in the activity of many *UGT1A* isoforms, thus resulting in the adverse effects of various drugs.[77] Table 4 presents the glucuronidation activity of UGT1As for 1091TT and 1456GG toward certain drugs. For example, glucuronidation activity toward the acetaminophen of p.Phe364Leu–UGT1A1A9 was 5.0% of the wild type and glucuronidation activity toward the 2-amino-5-nitro-4-trifluoromethylphenol (a major metabolite of flutamide) of p.Tyr486Asp-UGT1A6 was <1% of the wild type.[77,78] Therefore, the gene analysis of variations on common exons in patients who experience adverse effects of drugs can help determine the significance of the variations.[77,79]

5 | THERAPEUTIC RESPONSE: INVOLVEMENT OF *UGT1A1* IN GILBERT'S SYNDROME, CRIGLER–NAJJAR SYNDROMES, AND IRINOTECAN PHARMACOGENETICS AS EXAMPLES

5.1 | Glibert's syndrome

Because the UGT1A1 enzyme activity is approximately 30% of normal and considerably elevated bilirubin levels are not observed, patients with GS require no treatment.[80] However, patients with GS and other types of diseases should receive personalized treatment and care.[80] In order to maintain health-related quality of life, some scholars suggest to screen, counsel, monitor, and healthcare for GS subjects in anesthesia, direct antiviral therapy treatment, pregnancy, childbirth, surgery, and weight loss programs.[80]

5.2 | Crigler–Najjar syndromes

Two main categories of treatments are available for patients with CN: controlling bilirubin and its neurotoxic effects through phototherapy, plasmapheresis, and pharmacological treatment and restoring UGT1A1 activity in hepatocytes through cell and gene therapy.[81] Intensive phototherapy is a common treatment for CN-1.[81] Plasmapheresis is the most effective process for the removal of excess unconjugated bilirubin in patients with severe hyperbilirubinemia.[81] In patients with CN-2, pharmacological treatment includes the use of enzyme-inducing agent (phenobarbital), bilirubin-binding agents (calcium phosphate and orlistat), choleretics (ursodeoxycholic acid), and heme-oxygenase inhibitor.[81]

Although liver transplantation is the only therapeutic and definitive treatment for CN-1, the transplantation of allogeneic hepatocytes or hepatocyte progenitor cells and gene therapy (e.g., recombinant adeno-associated virus vectors) can cure such inherited liver disorders.[81]

5.3 | Irinotecan pharmacogenetics

Irinotecan is one of the most widely used anticancer agents. Many studies have reported the relationship between the glucuronidation of irinotecan and the variants of *UGT1A1* in Asians. For example, at least 18 studies on this topic have been published from 2018 to 2021 when irinotecan-based chemotherapy was prescribed for Asian patients with colon cancer.[82–99]

Patients with homozygous or heterozygous *UGT1A1* variants exhibited a lower glucuronidation ability for metabolizing irinotecan and then developing ADRs than did patients without *UGT1A1*

TABLE 4 Glucuronidation activity of UGT1As (V_{max} value, % of the corresponding wild-type) for the SNVs (1091TT and 1456GG) toward certain drugs

UGT1	A1	A3	A6	A7	A8	A9	A10
1091TT[77]							
β-estradiol	36.3	82.1	–[a]	26.8	29.2	–	22.5
Acetaminophen	50.3	–	46.4	17.2	44.1	5.0	42.8
Propofol	–	–	–	44.0	49.8	29.0	71.1
1456GG[78]							
Propofol	–	–	–	–	–	28.8	–
Mycophenolic acid	–	–	–	–	–	33.6	–
1-Naphthol	–	–	–	–	–	126.1	–
Naringenin	–	–	–	–	–	77.9	–
2-Amino-5-nitro-4-trifluoro-methylphenol	12.0	–	<1.0	–	–	–	–

Abbreviations: SNV, single-nucleotide variant; UGT, UDP-glucuronosyltransferase.
[a]Data not available.

variants.[2,93] The majority of those 18 studies have reported that both 211G>A and −53A(TA)$_6$TAA>A(TA)$_7$TAA were significantly associated with both irinotecan-induced toxicity and poor therapeutic efficacy (e.g., decreased progression-free survival). A study indicated that reducing the initial dose of irinotecan by approximately 20% might be safe without reducing the therapeutic effect in Japanese patients with colon cancer with homozygous *UGT1A1* variants.[92] The results indicate that pretherapeutic testing for the *UGT1A1* genotype in patients with cancer can improve patient safety and is a practical and cost-effective strategy, and such testing should become the standard of care.

We examined whether the 18 studies reflected the actual variation status of participants because most of the studies focused only on 211A and −53A(TA)$_7$TAA. We investigated the effects of both *UGT1A1* 211GA and −3279GG on the ADRs of cancer chemotherapy. In a review of Asian patients with colon cancer treated with irinotecan, ADRs, including severe ADRs, tended to be higher in patients with the 211GA genotype than in those with the wild-type genotype.[87]

The UGT1A1 activity for −3279GG was determined to be 60.0% of normal[44] and the same as that for 211GA (60.2% of normal[71]) We speculated that patients with cancer who harbor the *UGT1A1*–3279GG genotype would develop ADRs, as would patients harboring the 211GA genotype. The SNPs −3279GG and 211G>A are two independent variants because of the expulsion phenomenon. A study reported that *UGT1A1*–3279GG and *UGT1A1* 211G>A genetic variants are independent factors affecting the occurrence of grade 3–4 delayed diarrhea in Chinese patients with cancer receiving treatment with irinotecan (50.4% of them had colon cancer).[99] The findings indicated that *UGT1A1*–3279GG should not be neglected in pharmacogenetic studies.

6 | CONCLUSION

Variants of *UGT1A1* not only play a critical role in the development of CN, GS, and neonatal hyperbilirubinemia but are also involved in the development of ADRs and in the clinical efficacy of chemotherapy. The SNV −53A(TA)$_6$TAA>A(TA)$_7$TAA in *UGT1A1*, which was first reported by Dutch scholars in 1995,[1] has been observed in Asian populations since 1996.[41] In addition, the SNVs 686C>A, 211G>A, 1456T>G, and −3279T>G were first identified by Japanese investigators in 1995,[1] 1998,[71] and 2002,[44] whereas 1091C>T was first determined by Taiwanese researchers in 2000.[13] The variation status of *UGT1A1* in Asians is more complicated than that in non-Asians. Therefore, examining *UGT1A1* in Asian populations is challenging. Comprehensive approaches should be adopted in future studies examining the involvement of *UGT1A1* in pharmacogenetics for Asian populations.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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