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PharmGKB summary: very important pharmacogene information for UGT1A1

Julia M. Barbarino^a, Cyrine E. Haidar^c, Teri E. Klein^a, and Russ B. Altman^b

^aDepartment of Genetics, Stanford University, Palo Alto, California, USA

^bDepartment of Bioengineering, Stanford University, Palo Alto, California, USA

^cDepartment of Pharmaceutical Sciences, St Jude Children's Research Hospital, Memphis, Tennessee, USA

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Introduction

The uridine diphosphate glucuronosyltransferase (UGT) enzymes are a superfamily of enzymes responsible for the glucuronidation of target substrates. The transfer of glucuronic acid renders xenobiotics and other endogenous compounds water soluble, allowing for their biliary or renal elimination [1]. The UGT family is responsible for the glucuronidation of hundreds of compounds, including hormones, flavonoids, and environmental mutagens [1]. Most of the members of the UGT family are expressed in the liver, as well as in other types of tissues, such as intestinal, stomach, or breast tissues. A few members are expressed only extrahepatically, such as UGT1A7, UGT1A8, UGT1A10, and UGT2A1 [2]. Four families exist within the UGT superfamily: UGT1A, UGT2, UGT3, and UGT8 [3]. UGT2 is further divided into two subfamilies, UGT2A and UGT2B, both of which are present on chromosome 4 [2]. UGT2A enzymes are involved in the glucuronidation of compounds such as phenolic odorants and polycyclic aromatic hydrocarbon metabolites, although limited studies have been carried out on this subfamily [4]; UGT2B proteins are mainly responsible for the metabolism of steroids [5]. The roles of UGT3 and UGT8 family members have not been well characterized [3]. The UGT1A family is located on chromosome 2q37, and the members of this group glucuronidate a large variety of compounds. Pharmaceutical drugs are a common substrate of the UGT1A family [1], making the enzymes in this group relevant to pharmacogenetic research. This very important pharmacogene summary on

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Correspondence to Teri E. Klein, PhD, Department of Genetics, 1501 California Avenue, Stanford University, Palo Alto, CA 94304, USA, Tel: + 1 650 736 0156; fax: + 1 650 725 3863; teri.klein@stanford.edu.

Conflicts of interest

There are no conflicts of interest.

UGT1A1 is available with interactive links to genetic variants and drugs on the PharmGKB website at <http://www.pharmgkb.org/gene/PA420>.

The *UGT1A* gene locus

The *UGT1A* gene locus enables the transcription of nine unique enzymes: UGT1A1 and UGT1A3 through UGT1A10 [1,6]. This occurs by exon sharing, in which one of nine unique exon 1 sequences at the 5' end of the gene is combined with the common exons 2–4 and 5a at the 3' end, forming individual *UGT1A* transcripts [7–9] (Fig. 1). Alternatively spliced isoforms of UGT1A exist and are formed when exon 5b (seen in the common exon region) is used instead of, or in addition to, exon 5a [10]. These alternative isoforms are known as isoforms 2 or UGT1As_i2 and are enzymatically inactive [10,11]. In addition, four UGT1A pseudogenes exist: *UGT1A2p*, *11p*, *12p*, and *13p* [7,12]. These pseudogenes can be seen in Fig. 1, along with the location of two principal UGT1A1 pharmacogenetic variants, *28 and *6, both of which are discussed in detail further on within this summary.

UGT1A1

UGT1A1 function

One of the transcripts encoded by the UGT1A locus is *UGT1A1*, which is at the furthest 3' end of the *UGT1A* exon 1 region. *UGT1A1* is expressed hepatically as well as within the colon, intestine, and stomach [13,14]. One of the main functions of UGT1A1 lies within the liver, where it is the sole enzyme responsible for the metabolism of bilirubin, the hydrophobic breakdown product of heme catabolism [1,15]. In general, UGT1A enzymes have considerable overlap in substrate specificities [16]; however, no other enzyme can substitute for the bilirubin glucuronidation activity of UGT1A1 [1]. In addition, no effective alternative pathways exist for the detoxification and elimination of bilirubin, excluding photoisomerization, a relatively inefficient pathway compared with UGT1A1 glucuronidation [17]. Patients with Crigler–Najjar type I (CN1) disease (discussed below) act as models for this concept: they are either homozygotes nor compound heterozygotes for inactive enzyme variants and are also incapable of glucuronidating or eliminating bilirubin [18].

UGT1A1 variants

Currently, 113 different *UGT1A1* variants have been described throughout the gene. These variants can confer reduced or increased activities, as well as inactive or normal enzymatic phenotypes. These individual variants are described as alleles by the UGT nomenclature committee (http://www.pharmacogenomics.pha.ulaval.ca/cms/ugt_alleles/) and are denoted by the * symbol followed by a number.

UGT1A1 alleles and their role in disease

Homozygotes or compound heterozygotes for inactive *UGT1A1* alleles have a complete absence of bilirubin glucuronidation and removal, leading to a high serum level of unconjugated bilirubin (hyperbilirubinemia), and a serious condition known as Crigler–Najjar type I disease [1]. If left untreated, CN1 is invariably fatal [19]. The development of

hyperbilirubinemia results in kernicterus, or the buildup of bilirubin within brain tissue. This causes irreversible neurological damage, leading to severe disability or death. Intensive phototherapy can keep bilirubin levels in check, but it becomes less effective with age, and the only definitive treatment is liver transplantation [17].

Crigler–Najjar type II also results from mutations within the *UGT1A1* gene, but some residual enzymatic activity remains, conferring a milder phenotype [19]. This type can be treated successfully with phenobarbital, which induces the expression of UGT1A1, allowing for reduction of unconjugated bilirubin to innocuous levels [20–22]. Kernicterus may still develop, however, if bilirubin levels are enhanced, such as during sepsis or trauma [19].

Gilbert's syndrome represents the least severe of the inherited unconjugated hyperbilirubinemia conditions [23] and results from UGT1A1 glucuronidation activity that is ~30% of normal [24]. Patients with Gilbert's syndrome have fluctuating bilirubin levels, which are often within the standard range [24]. Illness, stress, or fasting can precipitate a rise in bilirubin levels, leading to hyperbilirubinemia and symptoms such as jaundice or abdominal discomfort. However, these symptoms will typically resolve themselves, and the syndrome is harmless in adults [24]. Children are usually asymptomatic and are typically diagnosed during adolescence because of the manifestation of mild hyperbilirubinemia [25]. Although the condition is benign in itself, it is an indicator of reduced UGT1A1 activity, and it is therefore important to consider in the context of drug toxicity. Gilbert's syndrome can be caused by a variety of genetic changes, but within White and African-American populations it is most commonly attributed to the *UGT1A1**28 variant allele (rs8175347) [26]. This allele is characterized by seven thymine–adenine (TA) repeats within the promoter region, as opposed to six that characterize the wild-type allele (*UGT1A1**1) [27]. This extra repeat impairs proper transcription of the gene, resulting in a decrease in the transcriptional activity of the gene by ~70% [24,28]. The *UGT1A1**37 allele has eight TA repeats at this site and results in a reduction in promoter activity to levels lower than that in the promoter with the *UGT1A1**28 allele [26]. In contrast, the *UGT1A1**36 allele has only five repeats and is associated with increased promoter activity of the gene and a reduced risk for neonatal hyperbilirubinemia, a common and typically benign condition [26,29]. In Asian populations, the *UGT1A1**6 allele is more common [30]. This variant results from a glycine to arginine change at position 71 within the coding region (Arg71Gly; 211 G > A; rs4148323) [31]. Individuals homozygous for this allele also have enzymatic activity at ~30% of normal and can present with Gilbert's syndrome [32], as well as neonatal hyperbilirubinemia [33].

UGT1A1 alleles have also been associated with the development of various cancers. Along with bilirubin and pharmaceuticals, UGT1A1 enzymes have been seen to glucuronidate benzo(α)pyrene-*trans*-7,8-dihydrodiol, a precursor to the potent carcinogen benzo(α)pyrene-7,8-dihydrodiol-9,10-epoxide, which is found in charbroiled food, coal tar, and cigarette smoke [34]. They have also been noted to glucuronidate estradiol [35], as well as 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP), another carcinogen present in cooked meat [36]. UGT1A1 therefore exhibits a protective effect against benzo(α)pyrene-mediated and PhIP-mediated carcinogenicity, and modulates levels of estradiol within the body [34–36]. The *28 allele has been shown to increase the risk of developing colorectal

and breast cancer across multiple studies in Chinese and White populations [37-39]. The *6 allele was seen to increase the risk for colorectal cancer in one study in a Chinese cohort [40]. As these alleles reduce UGT1A1 activity, any associations seen are potentially due to increased exposure to carcinogens and estradiol [1]; increased levels of the latter are associated with the development of breast cancer [41]. However, several studies have shown no associations between the *28 allele and risk for breast cancer [42,43], and one showed a decreased risk for breast cancer in *28 carriers [44].

There is also evidence suggesting that the UGT1A1 *28 allele may offer protection from cardiovascular disease (CVD). Bilirubin is a known antioxidant and is thought to be capable of preventing plaque formation that leads to atherosclerosis [45]. Multiple studies have found a link between low bilirubin concentrations and an increased risk for CVD [46], although this association may be affected by confounders such as obesity or cholesterol levels [46,47]. As the *28 allele impairs transcription of the *UGT1A1* gene, it is associated with significantly increased bilirubin concentrations and therefore could be an important biomarker for predicting those at decreased risk for CVD [48]. In addition, testing for associations between the *28 allele and CVD allows for a Mendelian randomization approach, which helps avoid confounding and reverse causation, limitations present in the studies linking bilirubin levels with CVD [47,49]. A 2006 study utilizing the Framingham Heart Study population followed 1780 individuals for 24 years, and found that those with the *28/*28 genotype were at one-third the risk for CVD as compared with those with the *1/*28 or *1/*1 genotypes [50]. However, additional studies and meta-analyses [46,51], including one with over 67 000 participants (analyses in this study were carried out using the rs6742078 variant, shown to be in strong linkage disequilibrium with rs8175347) [49], have failed to find a link between the *28 allele or bilirubin levels and the risk for CVD or myocardial infarction.

UGT1A1 allele frequencies

Both *UGT1A1**36 and *UGT1A1**37 alleles occur almost exclusively in populations of African origin, with estimated allele frequencies of 0.03–0.10 and 0.02–0.07, respectively [26,52,53]. *UGT1A1**28 occurs with a frequency of 0.26–0.31 in Caucasians, 0.42–0.56 in African Americans, and only 0.09–0.16 in Asian populations [26,52]. *UGT1A1**6 has allele frequencies of 0.13, 0.23, and 0.23 in Japanese, Korean, and Chinese populations, respectively [30].

UGT1A1 pharmacogenetics

Both the *28 and *6 alleles have been well studied with regard to pharmaceutical toxicities. In particular, both alleles have shown associations with the development of irinotecan toxicities [54-56]. Irinotecan is a topoisomerase I inhibitor and an analog of the naturally occurring alkaloid camptothecin [57]. It is primarily used to treat colorectal cancer, although it is also used to treat solid tumors within other organs [57]. As a prodrug, irinotecan is converted by carboxylesterases to SN-38, a metabolite that has 100-fold higher antitumor activity than its parent compound [58]. UGT1A1 is the predominant isoform responsible for the glucuronidation of this toxic metabolite, enabling its eventual excretion. However, in-vitro studies have shown that UGT1A7 and UGT1A9 are also involved in SN-38

glucuronidation [59]. Irinotecan has a very narrow therapeutic range, and treatment can lead to a variety of side effects, mainly neutropenia and diarrhea, which can be severe enough to reduce dosage or discontinue the drug [60]. Indeed, ~7% of patients undergoing irinotecan treatment and presenting with severe neutropenia and fever die from these complications [61]. Several studies have also shown that genotyping for the *28 allele before irinotecan treatment for colorectal cancer is cost-effective [61,62], which suggests that testing for this allele may have a place in clinical practice.

Besides that of irinotecan, UGT1A1 is also responsible for the glucuronidation of drugs such as raloxifene [63] and etoposide [64], and some associations have been reported between the *28 allele and pharmacokinetic and pharmacodynamic parameters of these drugs [64,65]. In addition, the development of hyperbilirubinemia during treatment with inhibitors of UGT1A1, such as atazanavir and tranilast, has also been linked to the presence of the *28 allele [66,67].

It has been suggested that including variants from other UGT1A isoforms may lead to stronger associations with drug side effects and pharmacokinetic measures. UGT1A7 shows a five-fold higher specific activity for the SN-38 metabolite than UGT1A1 [59,68], and the inclusion of *UGT1A7* alleles into association studies with irinotecan toxicity have shown persuasive results: the combination of *UGT1A1**28 with *UGT1A7**2 and *UGT1A7*-57T/G alleles was superior for prediction of neutropenia and dose reduction, as compared with the *UGT1A7* or *UGT1A1**28 alleles alone. Indeed, the *UGT1A1**28 allele by itself showed no association with neutropenia or dose reduction in this particular study [60]. The *UGT1A7* alleles analyzed were associated with a reduction in either glucuronidation activity or transcription activity, providing a mechanistic explanation for the increased risk for toxicity observed [60]. A later study by Cecchin *et al.* [69] found that in multivariate analyses, *UGT1A7**3 was the only significant predictor of hematologic toxicity in the first cycle of treatment with FOLFIRI (fluorouracil, leucovorin, and irinotecan); *UGT1A1**28 was not a predictor of toxicity. Another study by Lévesque *et al.* [70] in patients taking FOLFIRI found in multivariate analyses that *UGT1A7**4 (rs11692021) and *UGT1A6**5 (rs2070959) were both significant predictors of neutropenia, whereas *UGT1A1**28 was not. *UGT1A7**4 is associated with a reduction in glucuronidation activity [59,71], which may explain its association with increased risk for neutropenia. UGT1A6 has been shown to glucuronidate SN-38 [59,68], although no information is currently available on how the *5 allele may affect the enzyme. The study also found a dosage effect when considering multiple alleles: assessing *UGT1A7**4 and *UGT1A6**5 together as a haplotype gave an odds ratio of 2.18 for the development of neutropenia; including the *UGT1A9*-688A/C variant allele in the haplotype increased the odds ratio to 5.28. This result suggests that considering multiple *UGT1A* variants may improve risk prediction for neutropenia [70]. In patients taking atazanavir, Lankisch *et al.* [67] found that the combination of the *UGT1A1**28, *UGT1A7*-57G, *UGT1A7**2, and *UGT1A3*-66C variants was associated with an increased risk for jaundice and hyperbilirubinemia. Approximately 20% of atazanavir-treated patients were homozygous for this haplotype, compared with 40% of atazanavir-treated patients who presented with grade 3 or 4 hyperbilirubinemia – a statistically significant difference. All patients with exclusively grade 4 hyperbilirubinemia were homozygous for the haplotype

[67]. However, it remains uncertain how variants of UGT1A isoforms that are not directly involved in bilirubin metabolism lead to a propensity for atazanavir-induced hyperbilirubinemia [67]. The alleles present in this study were not in linkage disequilibrium [67], but variants within the UGT1A gene cluster often do show high levels of linkage [69]. This suggests the need for more haplo-type-based studies, which can determine interactions among *UGT1A* variants and potentially provide better predictions of drug toxicities [69].

Important variants

***UGT1A1*: *28 (7-TA insertion in promoter; rs8175347)**

The *UGT1A1**28 allele has been linked to side effects from irinotecan treatment such as neutropenia and diarrhea, although some studies have seen negative results for both phenotypes [72-74]. However, in 2004 the US Food and Drug Administration recommended on the irinotecan drug label that homozygotes for the *28 allele receive a lower starting dose of the drug [75]. A 2010 meta-analysis of 1998 patients found that the *28/*28 genotype was associated with an increased risk for neutropenia in patients taking low ($< 150 \text{ mg/m}^2$), medium ($150\text{--}250 \text{ mg/m}^2$), and high ($> 250 \text{ mg/m}^2$) doses of the drug, compared with those with other genotypes [54]. However, an earlier meta-analysis found that patients with the *28/*28 genotype had a higher risk for neutropenia compared with the other genotypes only at medium or high doses; *UGT1A1**28/*28 patients taking low doses had a similar risk to wild-type homozygotes [55]. Indeed, the Dutch Pharmacogenetics Working Group recommends only adjusting irinotecan dose for *28 homozygotes if the dose is greater than 250 mg/m^2 , upon which it should be reduced by 30% to avoid complications from neutropenia or diarrhea. Below this, no recommendations have been made [76].

A prospective study in metastatic colorectal cancer patients administered irinotecan found that not only was the *28 polymorphism associated with a higher risk for neutropenia, but homozygotes for this allele have a higher tumor response rate and a reduced risk of progression, compared with wild-type homozygotes. However, this did not have a significant impact on patient survival [77].

Studies linking *28 with diarrhea during irinotecan treatment have revealed mixed results [73,74,78,79]. However, a 2010 meta-analysis including 1760 cancer patients across 20 trials found that *28 homozygotes administered medium and high doses of irinotecan had a greater risk for severe diarrhea. There was also an association observed between heterozygotes administered medium and high doses of irinotecan and severe diarrhea. No associations were observed at low doses ($< 125 \text{ mg/m}^2$) [54]. Consistent findings have been observed in pediatric patients: Stewart *et al.* [80] found no association between the *28 allele and occurrence of diarrhea or neutropenia in children receiving low-dose irinotecan (between 15 and $75 \text{ mg/m}^2/\text{day}$).

*28 has also shown associations with hyperbilirubinemia during treatment with atazanavir or indinavir, antiretro-viral protease inhibitors and UGT1A1 inhibitors used for the treatment of HIV infections [67,81]. Rotger and colleagues found that Swiss patients homozygous for *UGT1A1**28 were more likely to develop hyperbilirubinemia and subsequent jaundice when treated with atazanavir or indinavir. The hyperbilirubinemia was not high enough to cause

any serious adverse effects, but it was stated that the jaundice could be stigmatizing and require additional consults and treatment modifications if the patient wished to discontinue the drug [82]. Other studies in different populations such as Koreans [83] and Brazilians [84] show similar associations between the *28 allele and atazanavir-associated hyperbilirubinemia and jaundice.

UGT1A1: *6 (Gly71Arg; rs4148323)

Unlike other *UGT1A1* alleles such as *60 (rs4124874) and *93 (rs10929302) [85], *UGT1A1* *6 is not in linkage disequilibrium with *28 [86], and thus likely has an effect on drug toxicity independent of the *28 allele. Although some studies have found no association with irinotecan side effects [87], several studies within Asian populations have found results suggesting that patients either heterozygous or homozygous for the *6 allele have a higher risk for neutropenia, diarrhea, dose modifications, and increased exposure to the cytotoxic SN-38 metabolite [56,88-90]. This indicates a potential role for the *6 allele in the prediction of irinotecan-induced toxicities. These studies were conducted in Japanese [56,89], Chinese, and Malay [90] populations, with a variety of different cancers. In two of the studies, the *UGT1A1* *28 allele was also analyzed and showed no associations with irinotecan side effects or pharmacokinetics [56,90]. However, this may have been because of the minor presence of *28 homozygotes in both study populations: Onoue *et al.* studied only one patient with the genotype [56], and Jada *et al.* studied none [90]. In addition, in the study by Onoue *et al.* [56], patients were administered low doses of irinotecan (< 150 mg/m²): a 2007 meta-analysis found no association between the *28/*28 genotype and neutropenia if the patients were taking doses of less than 150 mg/m² [55].

The *6 allele has also been associated with hyperbilirubinemia during treatment with indinavir. In Thai HIV patients, Boyd *et al.* found that heterozygotes with the *6 allele were at an increased risk for bilirubin levels reaching 'serious toxicity' (defined as > 2.5 mg/dl) compared with wild-type homozygotes. In addition, patients with one *6 allele and one or two *28 alleles showed an even greater risk for bilirubin levels increasing beyond 2.5 mg/dl, compared with the reference genotype. No significant increase in risk was seen for carriers of only the *28 allele [31].

Conclusion

Both the Food and Drug Administration and the Dutch Pharmacogenetics Working group suggest genotyping for the *UGT1A1* *28 allele before treatment with irinotecan. However, it is still unclear whether genotyping is relevant at all dosages of the drug. Genotyping for the *28 allele was shown to be cost-effective, and irinotecan toxicities can be life-threatening; hence, the variant appears to be a good candidate for clinical implementation. To make testing useful, more work needs to be carried out to assess the drug dose at which genotype affects the risk for severe neutropenia. It is also critical to then test whether modifying doses of the drug on the basis of genotype results in improved outcomes without any harmful effects, such as decreased tumor response. This could be accomplished by undertaking large prospective randomized trials, in which patient outcomes are compared between those receiving genotype-dictated dosages and those receiving standard recommended doses.

As Asian populations have a higher frequency of the *6 allele as compared with the *28 allele, it is important to conduct further studies on associations between *UGT1A1**6 and neutropenia or diarrhea. It is difficult to gauge the effect of either the *6 or *28 allele on diarrhea at this time point, as evidence remains conflicted. Genotyping for *UGT1A1**28 and *6 may also be useful for avoidance of potentially stigmatizing jaundice associated with the usage of certain drugs for HIV. When considering genotyping for avoidance of side effects, the impact of using alleles across multiple *UGT1A* isoforms cannot be discounted. *UGT1A* isozymes have overlapping substrate specificities within different tissues, and the predictive value of multiple alleles may far exceed that of *28 or *6 on its own. Future studies will hopefully be able to confirm the value of genotyping across multiple isoforms.

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Fig. 1.

A graphic representation of the human *UGT1A* locus (not drawn to scale). (a) The locus spans ~200 kbp and contains multiple alternative first exons, which together constitute exon 1. Each unique first exon has its own promoter site. The individual exons for each isoform are combined with the common exons 2–4 and 5a by splicing out any intervening sequence. Exons 2–4 and 5a are therefore present in every *UGT1A* isoform. However, alternatively spliced *UGT1A* isoforms do exist, and are known as isoforms 2 or *UGT1As_i2*; these are created when exon 5b is used instead of, or in addition to, exon 5a. An example of the formation of *UGT1A4* mRNA is also shown. In (a) the promoter for *UGT1A4* can be seen upstream of the gene, (b) shows the pre-mRNA formed after transcription, and (c) shows the final *UGT1A4* mRNA transcript after splicing. Although splicing occurring for common exons 2–5a has not been shown in this figure, it is important to note the absence of exon 5b in (c); this alternative exon has been spliced out to create the classical form of *UGT1A4*. The figure also shows the location of two important *UGT1A1* pharmacogenetic variants, *28 and *6, both of which are discussed in detail within this paper.