Uridine 5'-diphospho-glucronosyltrasferase: Its role in pharmacogenomics and human disease (Review)

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Abstract. Biotransformation is an enzyme-catalyzed process in which the body converts endogenous compounds, xenobiotics and toxic substances into harmless or easily excreted metabolites. The biotransformation reactions are classified as phase I and II reactions. Uridine 5'-diphospho (UDP)-glucuronosyltransferases (UGTs) are a superfamily of phase II enzymes which have roles in the conjugation of xenobiotics or endogenous compounds, including drugs and bilirubin, with glucuronic acid to make them easier to excrete. The method the human body uses to achieve glucuronidation may be affected by a large interindividual variation due to changes in the sequences of the genes encoding these enzymes. In the last five years, the study of the genetic variants of the UGTs at a molecular level has become important due to its association with several diseases and the ability to predict adverse events due to drug metabolism. In the present review, the structure and the prominent genetic variants of the UGT1A subfamily and their metabolic and clinical implications are described.

Contents

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1. Introduction

Biotransformation refers to a number of different enzyme-catalyzed processes, in which the body converts endogenous compounds, xenobiotics and toxic substances into harmless or easily excreted metabolites. These compounds may become active metabolites, inactive metabolic products, or metabolites with higher or lower activity (1,2).

The reactions associated with biotransformation are traditionally classified into two main groups. Phase I (non-synthetic) reactions are responsible for oxidation, reduction, hydrolysis and hydrogen removal reactions. These reactions typically occur in the liver. The oxidation reactions include cytochrome P450, nicotinamide adenine dinucleotide phosphate and oxygen. Phase II (conjugation) reactions are biosynthetic and require energy and certain cofactors. These reactions add a relatively large polar group (typically sulfate, amino acids, glutathione, methyl and glucuronic acid) to phase I reaction products (3). An alternative classification for biotransformation has been proposed according to the nature of the reaction as functionalization reactions and conjugation reactions. Whereas phase I reactions are associated with unmasking a polar functional group, phase II reactions link an endogenous polar group to a specific substrate (4).

In the majority of animal species, a set of enzymes catalyzes these conjugation reactions. The uridine 5'-diphospho (UDP)-glucuronosyltransferase (UGT) superfamily, which primarily catalyzes conjugation reactions, is one of these enzyme families. The UGT superfamily is located in the microsomal fraction of various tissues, including the liver, kidney, skin, intestine and brain and is quantitatively important in the liver. The catalytic reaction of the UGT superfamily is the incorporation of a glycosyl group (glucuronic acid, glucose, xylose or galactose) to a range of acceptors. A number of frequently used drugs are conjugated with glucuronic acid, which is synthesized from glucose in the soluble fraction of the liver (5).

UDP-glucuronic acid (UDPGA) serves as the glucuronic acid donor to various acceptors that consist of drugs and metabolites. Although glucuronidation frequently inactivates xenobiotics, there are exceptions, including morphine

and 12-retinoic acid, which become pharmacologically active. The conjugation with glucuronic acid is an important qualitative and quantitative reaction due to the number of substrates that can be modified and the wide availability of UDPGA (6,7).

2. UGTs

The human UGT superfamily is divided into four major families: UGT1, 2, 3 and 8, with the UGT1 and 2 families being most important for glucuronidation reactions. The UGT2 family is subdivided into two subfamilies (UGT2A and UGT2B). The function and catalytic activity of the UGT3 remains unknown and the UGT8 gene product is a UDP-galactose ceramide galactosyltransferase (8).

The role of the genetic variants of the UGT1 family, its associated syndromes and altered drug metabolism have been well documented. Changes in the nucleotide sequence may be located in the promoter, regulatory, intronic or coding regions. Specific genetic variants are associated with a number of pathologies are described in Table I (9-31) and those associated with drug metabolism are described in Table II (10,32-46).

UGT1A subfamily. The UGT1A subfamily is typically responsible for the conjugation of bilirubin, phenols, anthraquinones, flavones, estriol and estradiol (47). The UGT1A locus is located at 2q37.1 and it contains four common exons 2-5 and 13 alternative exons (A1-A13). All combinations of one alternative exon in addition to the four common exons have the potential to generate 13 transcription units (Fig. 1A). However, the UGT1A locus potentially encodes for only nine functional proteins: UGT1A1 and UGT1A3-10 as 1A2P, 1A11P-1A13P belong to pseudogenes that do not encode for proteins (9,48). For the mRNA 3' region, there are two alternative exons, termed 5a and 5b. Each of the nine potential coded protein RNA transcripts with A1-A13 exons have the possibility to include the 5a, 5b or 5a plus 5b variant exons, resulting in three possible mRNAs and three putative transcripts (49) (Fig. 1C). When only the 5a variant is incorporated at the mRNA 3' region; the mRNA is termed the V1 isoform and encodes for the catalytically active form. When the 5b or 5a plus 5b variants are incorporated, they form inactive isoforms termed v2 and v3, respectively (50). Thus, the 5b variant, alone or in combination with 5a, results in an enzymatically inactive protein, but it acts as a negative modulator of the 5a variant.

UGT1A1 isoforms. Variations in UGT1A1 have been studied and 136 allelic variants have been described. The variants were associated with diminished or absent enzyme activity, resulting in clinical implications. The ClinVar database contains a dataset with clinically significant variants (51).

Mutations in the UGT1A1 exons or promoter region produce structural or functional deficiencies in the enzyme, which may result in deterioration of the conjugation. A commonly described variant is the TA dinucleotide insertion in the TATA element of the gene promoter (Fig. 1B). The 7 TA repeats instead of the 6 normal TA repeats (UGT1A1*1) is designated the UGT1A1*28 allele. This variant is associated with Gilbert's syndrome (GS), prenatal hyperbilirubinemia and adverse events due to the metabolism of certain drugs, including irinotecan, FOLFIRI, atazanavir, tamoxifen, belinostat and acetaminophen (Tables I and II).

Besides the seven TA repeats variant in the UGT1A1 gene, there are additional 5 (UGT1A1*36) and 8 (UGT1A1*37) TA repeats. It has been demonstrated that the greater the number of repetitions, the lower the enzyme activity. Therefore, the 5, 7 and 8 repeat variants exhibit 130, 65 and 50% activity, respectively, compared with the normal 6 repeat version (Fig. 1B) (52). The 211G>A variant (Arg71Gly, UGT1A1*6 allele) in exon 1 has also been described and exhibits 30% of the normal activity. This variant affects the metabolism of 7-ethyl-10-hydroxycamptothecin (SN-38), an active metabolite of irinotecan, which is commonly employed in colon cancer treatment and associated with GS and neonatal hyperbilirubinemia (36,53). Genotyping patients with UGT1A1 variants is important and alerts must be taken into account for screening in pharmacogenomics and prior to certain drugs treatments, including irinotecan and atazanavir (10).

The two main diseases associated with UGT1A1 variants are Crigler-Najjar syndrome (CNS) type I (-I) and type II (-II) and GS. A previous review reported that these diseases were associated with 77 point missense mutations, 14 point nonsense mutations, 21 deletions, 10 insertions and 8 promoter/intronic mutations (polymorphisms) in the UGT1A1 gene (54).

3. Clinical disorders or pathologies associated with mutations in UGT1A1

Neonatal hyperbilirubinemia. A range of diseases are associated with bilirubin clearance, the majority of which are inherited (55); however, the elevation of serum bilirubin is a common finding during the first week of life. This phenomenon should be evaluated, as it may be a transitory condition that spontaneously resolves or a serious illness. Neonatal non-conjugated hyperbilirubinemia is a common condition in pediatric medicine. Hemoglobin is metabolized to heme and globin groups; heme becomes biliverdin, which in turn becomes bilirubin (non-conjugated). Bilirubin is conjugated with glucuronic acid in the liver, becoming conjugated bilirubin; the conjugated form returns to the water-soluble bilirubin molecule that may be excreted in bile (47). Failure in bilirubin conjugation leads to an increased level of non-conjugated bilirubin, which is less hydrosoluble and has the ability to cross the blood-brain barrier. Although non-conjugated hyperbilirubinemia usually is self-limiting and benign, occasionally the severe non-conjugated hyperbilirubinemia leads to encephalopathy or kernicterus. The causes of the non-conjugated hyperbilirubinemia may be excessive production of billirubin during a hemolytic process, inadequate clarification of bilirubin or a combination of the two (56).

In newborns, the UGT1A1*28 allele is associated with hyperbilirubinemia and jaundice. In Spain, a study of 136 newborns, 21 of them with jaundice, demonstrated that newborns with jaundice had a tendency to have a higher prevalence of the UGT1A1*28, but this result was not statistically significance (57). A Chinese study concluded that different variants in the UGT1A1 gene, including UGT1A1*6, UGT1A1*28 and minor allele T of rs887829, are associated with bilirubin levels in the first days of life (11). Long-term studies are necessary to identify any diseases associated with

Table I. Pathologies associated with certain UGT1A variants.

UGT genetic variant	Associated disease	(Refs.)
UGT1A1*28 extra TA repeat [A(TA)$_7$A], rs8175347	Gilbert's syndrome, neonatal hyperbilirubinemia, colorectal and breast cancer risk, protection from cardiovascular disease, increased need of oxygen supplementation and risk of bronchopulmonary dysplasia in very preterm newborns	(9-17)
UGT1A1*6, GLY71ARG (G71R), rs4148323	Neonatal hyperbilirubinemia, breast milk jaundice, Gilbert's syndrome, increased risk for colorectal and laryngeal cancer	(10,27-31)
R336W	Crigler-Najjar Syndrome (Type I)	(18,19)
UGT1A1 deletion of 4591 bp (2335 bp in 5'-UTR, exon 1 and 1377 bp in the intron 1-2)	Crigler-Najjar Syndrome (Type I) is due to complete and non-inductile deficiency of UGT1A1	(20)
UGT1A1 Y486D, p.G71R	Crigler-Najjar Syndrome (Type II) milder phenotype.	(21)
UGT1A7*3	Hepatocelular carcinoma, orolaryngeal, proximal digestive tract and colorectal cancer.	(22-26)

UGT, uridine 5'-diphospho-glucuronosyltransferase; rs, reference single nucleotide polymorphism identification number; UTR, untranslated region; bp, base pairs.

Table II. UGT variants associated with known or potential drug toxicity.

Drug	UGT variants	Effect and references
Irinotecan/SN-38	UGT1A1*28, UGT1A7*3, UGT1A7*12, UGT1A1-3156G>A G71R, P229Q, Y486D UGT1A7*4, UGT1A6*5, UGT1A9-688A/C	UGT low-function, neutropenia, severe diarrhea, dosage, efficacy and prognosis (10,32-39)
FOLFIRI (fluorouracil, leucovorin and irinotecan)	UGT1A7*3 UGT1A7*4 (rs11692021) and UGT1A6*5 (rs2070959)	Hematologic toxicity/neutropenia (10)
Atazanavir	UGT1A1*28, UGT1A7-57G, UGT1A7$^{N129K/R131K}$ UGT1A7*2, UGT1A3-66C	Increased risk for jaundice and hyperbiliru binemia (10,40,41)
Tamoxifen	UGT1A4-48Val, UGT2B7-268Tyr, UGT2B1-5523Lys	Effective plasma active tamoxifen metabolite levels (42,43)
Belinostat	UGT1A1*28, UGT1A1*60	Increased plasma concentrations, increased incidence of thrombocytopenia and neutropenia (44,45)
Acetaminophen	UGT1A 3´-UTR variant (rs8330)	Liver injury (46)

UGT, uridine 5'-diphospho-glucuronosyltransferase; rs, reference single nucleotide polymorphism identification number; UTR, untranslated region.

bilirubin or drug metabolism that patients may develop in the future.

GS. GS is a benign hereditary condition, typically diagnosed in adolescence. This disease is characterized by moderated non-conjugated or indirect hyperbilirubinemia, which is defined as a bilirubin concentration between 1 and 6 mg/dl. Bilirubin typically increases with fasting and in the presence of normal liver enzyme levels (47). It has been postulated that the homozygous UGT1A1*28 variant is necessary, but not sufficient, for the clinical expression of GS. In the general Caucasian population, ~15% are homozygous and 50% are heterozygous for the UGT1A1*28 polymorphism; however, only 10.3% are clinically diagnosed as patients with GS (9,58). This differential clinical manifestation may be associated with environmental factors and individual genetic variants that exert influence on global glucuronidation activity (41,59). GS has also been associated with defects in the conjugation of certain other compounds (60). Total bilirubin levels in patients with GS are also influenced by the -3279T>G variant (61).

CNS. Ciotti *et al* (62) reported that a patient with CNS-II exhibited a coding region alteration on each of the alleles of the *UGT1A1* gene: M310V and I431T, designated *UGT1A1*34* and UGT1A*35, respectively. This disease is associated with the metabolism of bilirubin and is caused by a total (CNS-I) or

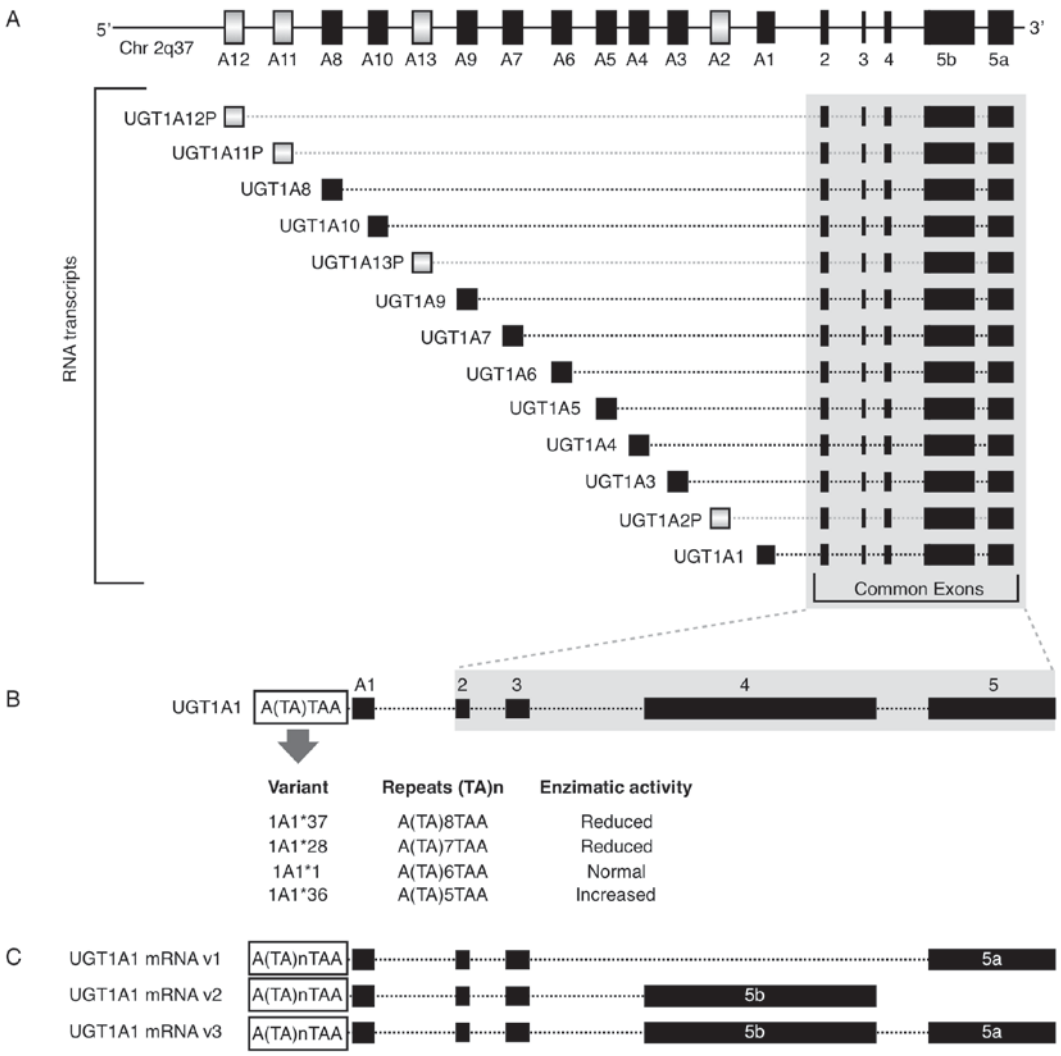

Figure 1. Graphical representation of the UGT1 locus. (A) The locus contains A1-A13 exons that are alternately spliced at the 5'-end of the mRNA and 2-5 common exons. Gradient-filled grey boxes correspond to pseudogenes, which do not encode for proteins. (B) UGT1A1 variants generated by the TA dinucleotide insertion/deletion in the TATA element at the A1 promoter and their effect on the enzymatic activity. (C) Alternative exon 5 (5a, 5b, or 5b plus 5a) at 3'-end of the mRNA, generating v1, v2 or v3 variants; v2 and v3 are inactive. Modified from Tourancheau *et al* (49). Solid black boxes correspond to genes. Black bordered boxes correspond to genes with a TA variant. Chr, chromosome; UGT, uridine 5''-diphospho-glucuronosyltransferases.

partial (CNS-II) deficiency of UGT1A1. In CNS-I and CNS-II, total serum bilirubin is between 30 and 50 mg/dl and between 6 and 20 mg/dl, respectively (63). Phenobarbital treatment reduces serum bilirubin levels by >30% and glucuronide bilirubin is present in the bile of patients with CNS-II. UGT1A1 is absent from patients with CNS-I. Genetic defects in patients with CNS-I are consistent with deletions, mutations or insertions of nucleotides of the UGT1A1 gene that result in premature stop codons or amino acid substitutions, which prevent mRNA transcription and lead to the autosomal recessive disease. In CNS-II the alteration is an amino acid substitution that results in reduced catalytic activity of UGT1A1 (18,64-66). A study conducted in unrelated Italian patients detected 22 mutations distributed along the gene (67). Large deletions are rarely reported in UGT genes, but they are reported in associated diseases. A large deletion encompassing the promoter region and exon 1 of the UGT1A1 gene was previously reported in a patient with CNS-I and the parents of the patient; the deletion covered 2,335 bp in the 5'-UTR, exon 1 and 1,377 bp in the 1-2 introns (20).

Cancer. UGT1A variants have been associated with an increased risk of developing colorectal, breast, laryngeal, orolaryngeal and proximal digestive tract cancer and hepatocellular carcinoma (Table I). The role of different types of UGT1A proteins in the metabolism of carcinogenic compounds is indirectly associated with the risk of cancer development. The UGT1A subfamily is responsible for the glucuronidation of carcinogenic tobacco compounds, such as benzo(α)pyrene (BaP). The BaP-trans-7R,8R-dihydrodiol [BPD(-)], the precursor of the mutagenic compound anti-(+)-BaP-7R,8S-dihydrodiol-9S,10R-epoxide, is primarily metabolized by UGT1A1 and UGT1A9 gene products; and both are expressed in the liver (10,68). Experiments conducted in normal liver microsomes isolated from individuals with *1/*1, 1*/28 and *28/28 genotypes revealed that bilirubin glucuronidation activity and BPD(-) glucuronide levels decreased, which suggests that the decreased activity of UDP glucoronosyltransferases serves a role in the detoxification of BaP and therefore, the risk of developing cancer (68).

UGT1A1*28 and UGT1A7 polymorphisms have been associated with the risk of colorectal cancer. The frequency of genotypes containing the UGT1A1*28 allele in the homozygous or heterozygous state was reported to be significantly higher in patients with colorectal cancer compared with controls (12). UGT1A7 is expressed in gastrointestinal and lung tissues. The UGT1A7 gene product is associated with the metabolism of carcinogens found in diets, including polycyclic or heterocyclic aromatic hydrocarbons and heterocyclic amines. A previous study demonstrated that UGT1A7*2 (Lys129, Lys131 and Trp208) and *3 (Lys129, Lys131 and Arg208) alleles are significantly associated with the risk of colorectal cancer and this is affected by alcohol intake and cigarette smoking (22).

Estrogen-sensitive cancers have been associated with the production of hydroxylated estrogen metabolites, termed catechol estrogens. Estradiol (E2) derived metabolites exhibit different biological properties. In breast cancer (BC), E2 and its oxidized and methoxylated metabolites are conjugated with glucuronic acid via the UGT1A1, 3 and 8-10 and 2B7 enzymes and these glucuronides are devoid of biologic activities. The genetic variants of these UGT genes may influence estrogen metabolism and the risk of BC (69,70). Also, a 150 kb deletion polymorphism in UGT2B17, which is considered a null genotype, inhibited the expression of the gene product and thus there was no enzyme activity. It has been reported that this null genotype is associated with BC; it has also been suggested that the UGT2B17 enzyme serves a role in cancer drug metabolism (71). Finally, a study reported that smoking or alcohol consumption combined with the G allele of the UGT1A1*6 gene (rs4148323 A/G) increased the risk of laryngeal cancer (27). Further examples of the association between cancer and UGT variants are cited in Table I.

4. The protective effect of bilirubin as antioxidant

The aforementioned genetic variants in the UGT families are associated with increased levels of plasma non-conjugated bilirubin. McCarty (72) previously suggested that bilirubin served a role as a potent antioxidant that scavenges superoxide, peroxyl radicals, hydroxyl radicals, hypochlorous acid, singlet oxygen and the reactive nitrogen species nitroxyl and peroxynitrite. Initially considered as a toxic compound, information has emerged regarding the protective role of moderately high levels of bilirubin, as observed in patients with GS and chronic diseases. Examples of the aforementioned protective role include an altered lipid profile and a reduced pro-inflammatory status (73), an inverse correlation between serum bilirubin concentrations and the risk of certain types of cancer (74) and a reduced risk of ischemic heart disease and hypertension (72).

5. Examples of UGT1A involvement in pharmacogenomics

Irinotecan metabolism. Irinotecan, an inhibitor of DNA topoisomerase I, is used to treat patients with metastatic colorectal cancer, which is a commonly diagnosed malignancy and one of the leading causes of mortality associated with cancer worldwide (75). Irinotecan has also been employed in ovarian (76), non-small lung cell (77) and pancreatic and biliary tract cancers (78). Irinotecan is prescribed alone, or combined with: i) 5-fluorouracil and Leucovorin (FOLFIRI), ii) FOLFIRI plus oxaliplatin, iii) Cetuximab, a chimeric immunoglobulin G1 anti-epidermal growth factor receptor monoclonal antibody (37,79), or iv) capecitabine (80). The combined effects of the genetic variants in these drug-metabolizing enzymes need to be considered to reduce undesirable effects and to increase the effectiveness of the drugs. Irinotecan is a prodrug that requires metabolism to the active form, SN-38, which has 100-fold higher antitumor activity, through carboxyesterases (10). SN-38 may subsequently be inactivated by UGT via glucuronidation (Fig. 2) (81,82). Severe toxicity has been reported in <36% of patients treated with irinotecan and the UGT1A1*28 allele is associated with toxicity in a dose-dependent manner. However, other UGTA1 variants may be associated with this toxicity (83).

Patients homozygous for UGT1A1*28 or UGT1A1*6 allele may receive irinotecan at an initial dose of 150 mg/m^2, but a reduction in the dose of subsequent cycles or a delay in the treatment is required (84). The aforementioned alleles have been associated with irinotecan-induced neutropenia in patients with colon cancer (85). Routine genotyping prior to chemotherapy has been used to prevent febrile neutropenia in patients with metastatic colorectal cancer at a reasonable cost (85). Furthermore, the administration of granulocyte-colony stimulating factor to patients with homozygous UGT1A1*28 may prevent the development of neutropenia (86). Finally, the UGT1A7 gene product, which is expressed in extrahepatic tissues, including the esophagus, stomach and lung, has been demonstrated to be associated with the metabolism of irinotecan to its non-toxic metabolite, SN-38 (87).

Pegvisomant (PEG-V) metabolism. PEG-V is a pegylated recombinant analog of human growth hormone (hGH), with covalently bonded polyethylene glycol polymer chains that reduce immunogenicity and the rate of clearance from the body, prolonging half-life (88). PEG-V is a modified version of hGH designed to bind to and inhibit the hGH receptor. In patients with acromegalia, PEG-V alone or in combination with a somatostatin analog has an efficacy of >90% for the control insulin-like growth factor (89,90). Liver injury has been reported with PEG-V in patients with Gilberts´Syndrome or the UGT1A1*28 genotype (91-94).

Atazanavir metabolism. The UGT1A1*28 allele is associated with atazanavir metabolism. The UGT1A1*28 allele, a low CD4 cell count and the presence of the G2677T/A variant of the multi-drug resistance gene (MDR)1, were independent risk factors for severe hyperbilirubinemia in Korean patients infected with human immunodeficiency virus, while the normal (MDR)1 and UGT1A1 alleles did not exhibit this condition (95). The UGT1A1*28 allele, a low CD4 cell count and the presence of the variant MDR1 G2677T/A in a 30 months follow-up study suggested that hyperbilirubinemia associated with atazanavir was common, but transient in Korean population that exhibit a low frequency of the UGT1A1*28 allele (96).

6. Conclusions

Studies continue to provide information regarding the association between the family of UGT enzymes, which are associated with the metabolism of drugs, xenobiotics and endogenous

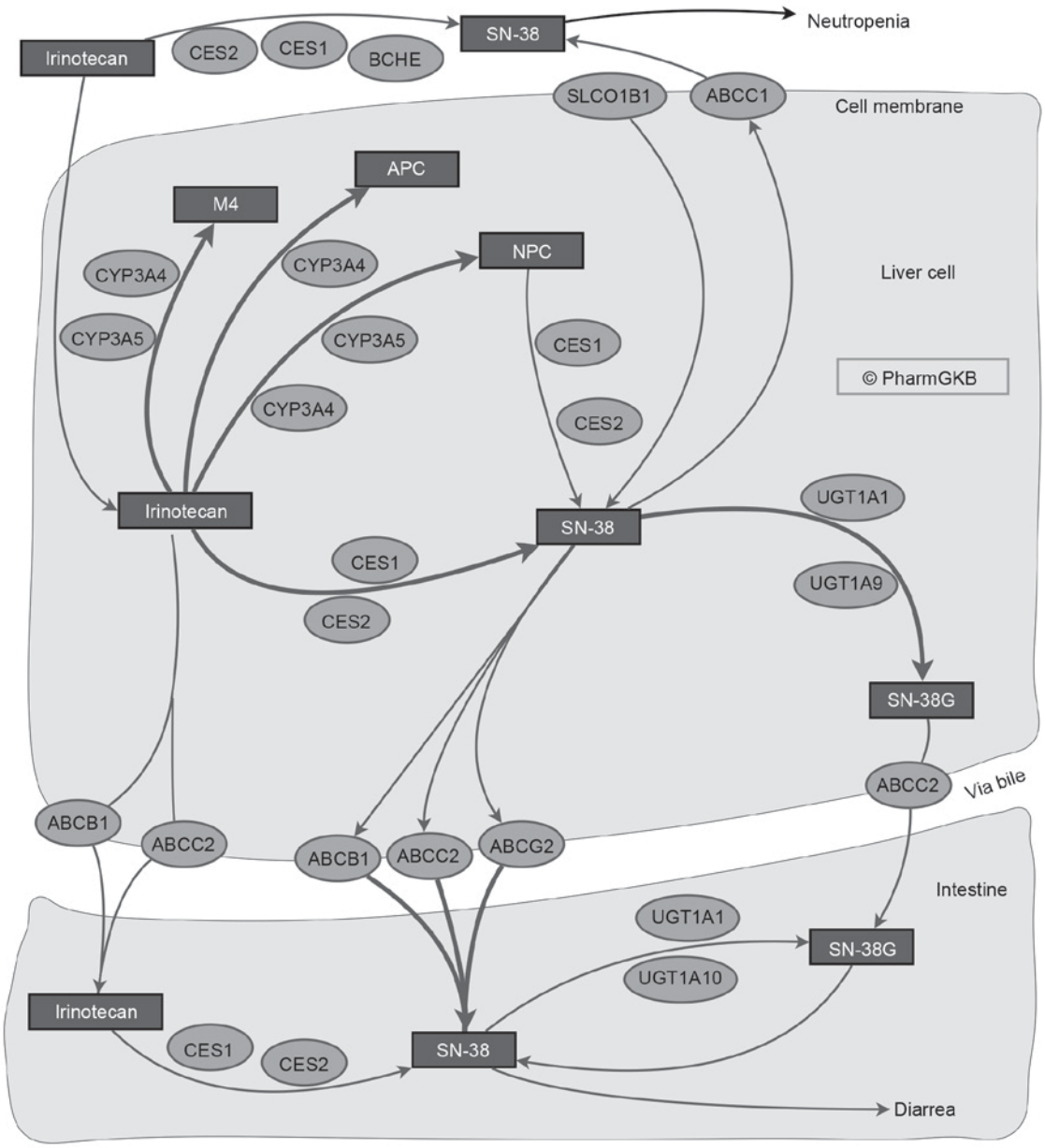

Figure 2. Irinotecan metabolism. Certain members of the UGT1A family are associated with the processing of SN-38. Reproduced with permission from the Pharmacogenomics Knowledge Base (PharmGKB) and Stanford University, a fully interactive version is available at: https://www.pharmgkb.org/pathway/PA2001 (81,82). CYP3A5, Cytochrome P450, family 3, subfamily A, polypeptide 5; ABCG2, ATP-binding cassette, sub-family G (WHITE), member 2; SLCO1B1, Solute carrier organic anion transporter family, member 1B1; BCHE, Butyrylcholinesterase; ABCB1, ATP-binding cassette, sub-family B (MDR/TAP), member 1; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1; CES2, Carboxylesterase 2; CYP3A4, Cytochrome P450, family 3, subfamily A, polypeptide 4; UGT1A10, UDP glucuronosyltransferase 1 family, polypeptide A10; UGT1A9, UDP glucuronosyltransferase 1 family, polypeptide A9; CES1, Carboxylesterase 1; ABCC2, ATP-binding cassette, sub-family C (CFTR/MRP), member 2; ABCC1, ATP-binding cassette, sub-family C (CFTR/MRP), member 1.

compounds and the effects of DNA variants on enzyme activity. In the current review, the importance of the UGT complex, which is associated with drug and xenobiotic metabolism and diseases associated with anomalies in the conjugation of bilirubin, was described. Also, the frequencies of genetic variants in population studies suggest that clinical significance depends on ethnicity. The diversity in the frequency of certain genetic variants by ethnicity may lead to a greater understanding of the role of patients' genetic backgrounds, the development of therapies according to pharmacogenomics profiles of patients and improved adverse event prediction due to drug metabolism. The pharmacogenomics profiles of UGT1A1 may improve the quality of life of patients, prevent adverse effects and reduce the cost of treating patients with associated diseases. The design of nanoparticles for the treatment of diseases, such as cancer, according to the pharmacogenomics profile and ethnicity of a patient is a notable opportunity for advancement in treatment options (97). In certain cases, the Food and Drug Administration has made changes to the labels of specific prescription drugs, such as irinotecan, warning that there may be a need for genotyping variants of UGT1A1 enzymes prior to the administration of the chemotherapeutic agent. In the future, the recommendation for individual genotyping prior to drug administration may often be prescribed.

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Authors' contributions

CNSD and ROL were responsible for the conception of the work, acquisition, analysis and interpretation of data for the review, drafting the work, revising it critically for important intellectual content, and gave final approval of the version to be published. MASS was responsible for the analysis and interpretation of data for the review, drafting the work and gave final approval of the version to be published. HLGB was responsible for the analysis and interpretation of data for the review, drafting the work, figure editing, permissions, revising it critically for important intellectual content, and gave final approval of the version to be published.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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