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# SULT genetic polymorphisms: physiological, pharmacological and clinical implications

**Katsuhisa Kurogi**[1,2], **Mohammed I. Rasool**[1,3], **Fatemah A. Alherz**[1,4], **Amal A. El Daibani**[1], **Ahsan F. Bairam**[1,5], **Maryam Abunnaja**[1], **Shin Yasuda**[1,6], **Lauren Wilson**[1], **Ying Hui**[1,7], **Ming-Cheh Liu**[1,*]

[1]Department of Pharmacology, College of Pharmacy and Pharmaceutical Sciences, University of Toledo Health Science Campus, Toledo, OH 43614 USA

[2]Biochemistry and Applied Biosciences, University of Miyazaki, Miyazaki 889-2192 Japan

[3]Department of Pharmacology, College of Pharmacy, University of Karbala, Karbala, Iraq

[4]Department of Pharmaceutical Sciences, College of Pharmacy, Princess Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia

[5]Department of Pharmacology, College of Pharmacy, University of Kufa, Najaf, Iraq

[6]Department of Bioscience, School of Agriculture, Tokai University, Kumamoto City, Kumamoto 862-8652, Japan

[7]Department of Obstetrics and Gynecology, Beijing Hospital, Beijing, China

## Abstract

**Introduction:** Cytosolic sulfotransferases (SULTs)-mediated sulfation is critically involved in the metabolism of key endogenous compounds such as catecholamines and thyroid/steroid hormones, as well as a variety of drugs and other xenobiotics. Studies performed in the past three decades have yielded a good understanding about the enzymology of the SULTs and their structural biology, phylogenetic relationships, tissue/organ-specific/developmental expression, as well as the regulation of the *SULT* gene expression. An emerging area is related to the functional impact of the *SULT* genetic polymorphisms.

**Areas covered:** The current review aims to summarize our current knowledge about the above-mentioned aspects of the SULT research. An emphasis is on the information concerning the effects of the polymorphisms of the *SULT* genes on the functional activity of the SULT allozymes and the associated physiological, pharmacological, and clinical implications.

[*]**Corresponding author:** Ming-Cheh Liu, Department of Pharmacology, College of Pharmacy and Pharmaceutical Sciences, University of Toledo Health Science Campus, 3000 Arlington Avenue, Toledo, OH 43614 USA, ming.liu@utoledo.edu.

Declaration of interest

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**Expert opinion:** Elucidation of how *SULT* SNPs may influence the drug-sulfating activity of SULT allozymes will help understand the differential drug metabolism and eventually aid in formulating personalized drug regimens. Moreover, the information concerning the differential sulfating activities of SULT allozymes toward endogenous compounds may allow for the development of strategies for mitigating anomalies in the metabolism of these endogenous compounds in individuals with certain *SULT* genotypes.

**Keywords**

Cytosolic sulfotransferase; SULT; sulfation; single-nucleotide polymorphism; SNP

## 1. Introduction

Biological sulfation in humans was first documented in 1876 with the detection of phenyl sulfate in the urine of a patient who was treated with phenol as an antiseptic [1]. This finding provided the initial clue that sulfation may play a role in the metabolism of xenobiotics. In line with this notion, many studies subsequently performed using experimental animals or human subjects have demonstrated the metabolism of drugs and other xenobiotics through sulfation [2,3]. It is generally accepted that sulfation may lead to the inactivation and/or facilitated excretion of xenobiotics. The enzymes responsible for catalyzing the sulfation reactions, now called the cytosolic sulfotransferases (SULTs) [4], however, were not identified until 1980 when two “phenol sulfotransferases” were isolated [5]. Interestingly, one of these two enzymes was found to display high affinity for dopamine and other catecholamines [6], indicating that sulfation may also play a role in the metabolism of endogenous compounds. It is now well documented that SULT-mediated sulfation is involved in the metabolism of not only catecholamines, but also thyroid and steroid hormones, as well as bile acids [7]. Sulfation of these endogenous compounds is believed to be involved in their homeostasis and/or transport in the body. Like other genes, genetic polymorphisms have been reported for the genes encoding SULTs [8–12]. In view of the physiological and pharmacological involvement of the SULTs, it is possible that the *SULT* genetic polymorphisms may predispose differential metabolism of catecholamines, steroid/thyroid hormones and other endogenous compounds, as well as xenobiotics including drugs, and therefore differential disease risks or clinical outcome for individuals with different *SULT* genotypes. This review aims to summarize our current knowledge about the SULTs, particularly the effects of the polymorphisms of the *SULT* genes on the functionality of the coded SULT allozymes and the possible resulting physiological/pharmacological implications. Figure 1 shows a typical SULT-mediated sulfation reaction. It is noted that during the reaction, the enzyme, SULT1A1, catalyzes the transfer of the sulfonate group from the co-substrate, 3’-phosphoadenosine 5’-phosphosulfate (PAPS), to the hydroxyl group of the substrate, acetaminophen.

## 2. Major classes of the SULTs and their roles in the metabolism of endogenous compounds and xenobiotics

Prior to the mid-1990s, the SULTs were mostly classified based on their substrate specificity and thus assigned names such as “monoamine”, “simple phenol”, or “estrogen”

sulfotransferases [5,6,13]. Such a nomenclature system, however, suffered from the overlapping substrate specificity among SULT enzymes. With the advent of molecular cloning and nucleotide/amino acid sequence analysis, it has become clear that the all SULTs across vertebrate species constitute a gene superfamily [4]. Among vertebrates, six gene families have been classified within the SULT gene superfamily [4,14,15]. Members of the same SULT gene family share at least 45% amino acid sequence identity. Within each SULT gene family, members of each subfamily share greater than 60% identity in amino acid sequence [4]. In humans, eighteen *SULT* genes, including five pseudogenes, have been identified and classified into five gene families [15]. Of the eighteen human SULT genes, twelve belong to the SULT1 family and comprise five subfamilies: SULT1A, SULT1B, SULT1C, SULT1D and SULT1E. Three belong to the SULT2 gene family with two subfamilies: SULT2A1 and SULT2B1. In contrast to SULT1 and SULT2 families, SULT3A1P, SULT4A1 and SULT6B1 contain only sole members in their respective families. Figure 2 shows a diagram illustrating the possible phylogenetic relationship between the eighteen human *SULT* genes. It is noted that SULT1D1P, SULT1D2P, SULT1C5P, SULT2A2P, and SULT3A1P are pseudogenes, with no corresponding protein products [15].

### 2.1. Human *SULT1* subfamily

Human *SULT1A* subfamily consists of 4 *SULT* genes, encoding 3 SULT isoforms: SULT1A1, SULT1A2, and SULT1A3. Sequence analysis revealed that *SULT1A3* and *SULT1A4* genes encode identical protein products, designated SULT1A3 [16]. Of the three SULT1A isoforms, SULT1A1 is known to play a pivotal role in the sulfation of phenolic xenobiotics, including polyphenols and number of drug compounds (cf. Table 1) [17,18]. *p*-Nitrophenol, naphthol, acetaminophen, and minoxidil are typical substrates of SULT1A1. SULT1A3 is known to be involved in the sulfation of monoamines and structurally related compounds (Table 1) [17,18]. Dopamine, serotonin, and isoproterenol are typical substrates of SULT1A3. Sulfation of phenolic compounds as mediated by SULT1A members plays an important role in the metabolism, and usually, the inactivation and excretion of the substrate compounds. It is noted, however, that the biological activity of minoxidil is activated upon sulfation [19].

Human *SULT1B1* is the sole member of *SULT1B* subfamily. The main physiological function of SULT1B1 has been proposed to be in the sulfation of thyroid hormones (Table 1) [20,21]. It is noted, however, that dopa and tyrosine have also been shown to be substrates for rat SULT1B isoform [22]. Sulfation of thyroid hormones is proposed to regulate the iodothyronine metabolism through iodothyronine deiodinase, since sulfated metabolites of thyroxine (T4) and triidothyronine (T3) undergo deiodination faster than unsulfated T4 and T3 [23].

Human *SULT1C* subfamily consists of 4 genes (including 1 pseudogene), encoding 4 SULT isoforms, SULT1C2, SULT1C3a, SULT1C3d, and SULT1C4. *SULT1C5P* gene is located between *SULT1C2* and *SULT1C4* and was originally designated *SULT1C2P*. In order to avoid redundant designation, the *SULT1C* pseudogene is designated *SULT1C5P* in this review. *SULT1C5P* contains some frameshifts, including start codon and the exons 2 -

5 and exons 6 - 7 [15]. SULT1C subfamily members have been proposed to catalyze the sulfation of some procarcinogenic compounds, e.g., N-hydroxy-2-acetylaminofluorene and hydroxybenzopyrene, leading to the activation of their carcinogenic activities [24–26]. Although the physiological substrates of SULT1C enzymes have not been fully elucidated, a number of endogenous and xenobiotic compounds have been reported to be sulfated by SULT1C enzymes (Table 1) [27]. Among these substrate compounds, thyroid hormones have been shown to be substrates for SULT1C2 [28]. SULT1C4 appeared to exhibit the broadest substrate specificity toward xenobiotic compounds including polyphenols and some drug compounds [27, 29–31]. Since the expression of human SULT1C subfamily members has been shown to be more prominent in fetal tissues, it has been suggested that SULT1C enzymes may play a role in the metabolism of xenobiotics and thyroid hormones during fetal development [24,27].

Human *SULT1E1* is the sole member of *SULT1E* subfamily. The main physiological function of SULT1E1 is believed to be in the sulfation of estrogens, including estrone ($E_1$) and 17β-estradiol ($E_2$) [13,32] (Table 1). Xenobiotic estrogen-like compounds such as 17β-ethynylestradiol (EE2) and daidzein have also been shown to be substrates for SULT1E1 [32–34]. Since estrogen sulfates are the major circulatory estrogens and can be hydrolyzed by steroid sulfatase, sulfation of estrogens has been proposed to play a pivotal role in the steroid homeostasis, in conjunction with the sulfatase pathway [32,35]. Therefore, the balance of sulfation and desulfation may be critical in the adjustment of estrogenic activity *in vivo*.

### 2.2. Human *SULT2* family

Human *SULT2* family comprises three subfamilies, *SULT2A* and *SULT2B*. *SULT2A1* is the sole member of the *SULT2A* subfamily. *SULT2A1* and *SULT2A2P* are paralogous genes. Of the two, *SULT2A2P* is a pseudogene which contains some frameshifts, including start codon and reversed order of exons 4 - 6 [15]. SULT2A1 is known to play a fundamental role in the metabolism of androgens and bile acids (Table 1) [36,37]. Steroid drugs such as budesonide and tibolone have also been shown to be substrates for SULT2A1 [38,39]. For endogenous androgens, sulfation has been shown to act as a reversible metabolic pathway, as in the case of estrogen metabolism [35]. Therefore, sulfation of androgens plays an important role in the deactivation and storage of androgens. It is worthwhile noting that estrogens are generated from androgens under the action of aromatase (CYP19A1), implying that sulfation of androgens by SULT2A1 may also affect the homeostasis of estrogens.

While human *SULT2B1* is the sole member of *SULT2B* subfamily, two N-terminal splice variants, SULT2B1a and SULT2B1b, have been reported [40,41]. SULT2B1a has been shown to play an important role in the sulfation of pregnenolone, while SULT2B1b is responsible for the sulfation of cholesterol. Similar to other steroid sulfates, pregnenolone sulfate and cholesterol sulfate are also hydrolyzed by steroid sulfatase, implying that the SULT2B1 isoforms play an important role in the homeostasis of steroid/sterol, in conjunction with steroid sulfatase [35]. Pregnenolone sulfate has been reported to act both as a neuromodulator and as a neurotransmitter via N-methyl-D-aspartate (NMDA) receptor and γ-aminobutyric acid type A (GABAA) receptors [42]. Sulfation of pregnenolone

may be a key factor in the learning and memory, as well as other synaptic functions. Cholesterol sulfate has been reported to act as a second messenger that functions in keratinocyte differentiation [43]. Besides, recent studies using the mouse model have shown that cholesterol sulfate may exert immune regulatory functions [44,45]. Sulfation of cholesterol has been suggested to be an important reaction that converts cholesterol to a signaling molecule. Therefore, the two SULT2B1 enzymes, SULT2B1a and SULT2B1b, appear to play multiple physiological roles, not just the deactivation and metabolism of steroids/sterols.

### 2.3. Human *SULT4* family

Human SULT4A1 is the sole member of the SULT4 family. Although a great many studies have been performed to investigate the enzymatic characteristics of SULT4A1, no substantial sulfating activity of SULT4A1 has been detected [27,46,47]. Therefore, SULT4A1 is now considered likely an orphan SULT, although it has been shown to be highly expressed in nervous system. In recent years, genetic analyses have suggested that mutation in the untranslated regions of *SULT4A1* gene may contribute to the etiology of schizophrenia [48,49]. Nevertheless, no mutations (synonymous or nonsynonymous) in coding regions of the *SULT4A1* gene have been found in schizophrenia patients [50]. More recently, *SULT4A1* knockout mouse or zebrafish models, have been developed to investigate the physiological relevance of SULT4A1 [51,52]. These animal studies have suggested that SULT4A1 may play a role in physical activity and behavior.

### 2.4 Human *SULT6* family

Human SULT6B1, the sole member of the SULT6 family, is likely an orphan SULT. No enzymatic activity of human SULT6B1 has been reported. In contrast, zebrafish, chicken, and mouse SULT6 enzymes have been shown to exhibit sulfating activities toward a variety of substrate compounds [53–55]. Zebrafish SULT6 showed strong sulfating activities toward simple phenols and polyphenols, while chicken SULT6 exhibited sulfating activities toward $E_2$ and corticosterone [53,54]. Mouse SULT6B1, on the other hand, displayed weak sulfating activities toward thyroxine and bithionol [55]. It thus appears that physiological functions of SULT6 may not be conserved among vertebrates and further studies are needed in order to elucidate any possible functions of human SULT6B1.

Table 1 shows the thirteen human SULTs with their polypeptide length, the chromosomal location of their coding genes, and their prototype substrates.

## 3. *SULT* genetic polymorphisms and functional implications

Like many other genes, single nucleotide polymorphisms (SNPs) occur for genes encoding the SULTs [8–12], and, significantly, *SULT* SNPs have been shown to be ethnically distributed [56]. *SULT* SNPs were first reported for the gene encoding human SULT2A1 (dehydroepiandrosterone sulfotransferase) [8], and has since been demonstrated for the genes encoding SULT1A1 [8], SULT1A2 [9], SULT1A3 [10], SULT1C2 [11], and SULT1E1 [12]. SNPs among the SULTs may lead to individual differences in the metabolism of both endogenous compounds and xenobiotics, including

drugs, through sulfation [9,11,56,57]. Such differences may correlate with the occurrence of certain pathophysiological conditions. For example, molecular epidemiology studies have demonstrated the correlations between certain *SULT1A1* SNPs and risks for cancers [58]. In view of the involvement of SULT-mediated sulfation in the metabolism of certain drugs, it is possible that *SULT* SNPs may also influence the metabolism of drugs in individuals with different *SULT* genotypes [58]. To understand better the correlations between *SULT* SNPs and particular disease states/risks or differential metabolism and, therefore, efficacy of drugs in different individuals, it is important to clarify their functional impact on the resulting protein products, i.e., SULT allozymes. To date, a number of studies have been performed to investigate the differential sulfating activity of different SULTs. The results obtained from these studies, as summarized in Table 2, are described in detail below. Table 3 summarizes the clinical relevance of human *SULT* gene polymorphisms and chromosomal mutations in respective *SULT* genes.

## *SULT1A1* SNPs and SULT1A1 allozymes

As noted above, SULT1A1 is one of the major SULTs involved in xenobiotic metabolism and detoxification [59, 60]. Pertaining to this important function is the ubiquitous expression of SULT1A1 in human tissues/organs [59, 60]. It has been reported that SULT1A1 exhibits the highest hepatic expression level among all SULT1 enzymes. SULT1A1 is also expressed, albeit at lower levels, in almost every extrahepatic organ/tissue, including brain, breast, gastrointestinal tract (GIT), kidney, platelets, and skin [61–63]. Furthermore, from a developmental biology perspective, SULT1A1 has been reported to be widely expressed at fetal stages [64–66]. The extensive expression during fetal development implies an essential role of SULT1A1 in the chemical defense during fetal development, through neonatal/child development, onto adulthood [66].

*SULT1A1* gene has long been recognized to have a polymorphic nature [8, 9, 67, 68]. Earlier studies revealed that SULT1A1 alleles encode allozymes with variations in not only the level of activity but also thermal stability [8, 60, 69]. Functional genomic studies have revealed that changes in nucleotide sequence could be translated into amino acid replacements with variations in enzyme function in the *SULT* gene family [8, 9, 70]. Distinct SULT1A1 allozymes were shown to be expressed as a result of single nucleotide polymorphisms (SNPs) in the *SULT1A1* gene [71]. Studies have demonstrated an alteration in the processing of xenobiotics, including therapeutic drugs, due to *SULT1A1* polymorphisms that influenced the SULT1A1 enzyme activity [72, 73].

Earlier studies have revealed a number of non-synonymous coding SNPs (cSNPs) of the *SULT1A1* gene, including *SULT1A1-R213H*, *SULT1A1*3* (M223V), *SULT1A1*4* (R37Q), and *SULT1A1*5* (F247L) [70, 74, 75]. Among these allelic variants, SULT1A1-R213H, which occurs in exon seven of the *SULT1A1* gene, appeared to be the most prevalent *SULT1A1* genetic polymorphism [60, 76]. The coded SULT1A1-R213H allozyme appeared to be less thermostable and displayed decreased binding affinity toward different substrate compounds, including some pro-mutagens, compared to the wild-type SULT1A1 [77]. A more recent study investigated the effect of nine missense *SULT1A1* cSNPs, *SULT1A1-R37Q*, *SULT1A1-P47S*, *SULT1A1-M77I*, *SULT1A1-H149Y*, *SULT1A1-Y169D*,

*SULT1A1-R213H*, *SULT1A1-T227P*, *SULT1A1-V243D*, and *SULT1A1-F247L*, on the sulfation of acetaminophen, *O*-desmethylnaproxen, and tapentadol [78]. Similar patterns of differential sulfating activities were found for the nine SULT1A1 allozymes towards all three drug compounds. Of the nine allozymes, SULT1A1-M77I and SULT1A1-F247L exhibited sulfating activities that were higher/comparable to that of the wild-type SULT1A1. The other seven SULT1A1 allozymes displayed lower specific activities than that of the wild-type enzyme, with SULT1A1-T227P showing the lowest activity [78]. It is noted that *SULT1A1-R37Q* and *SULT1A1-R213H* SNPs had also been identified in earlier polymorphic studies, which showed that the platelet samples corresponding to the *SULT1A1-R213H* genotype presented with a much lower sulfating activity than the platelet samples corresponding to wild-type *SULT1A1* genotype [8, 9, 71].

Some human population studies have revealed that the enzymatic activity of SULT1A1 in platelet differs by gender [79, 80]. Distinct allelic frequencies of some *SULT1A1* genotypes have been found in different ethnic groups [76, 81]. The allele occurrence of *SULT1A1-R213H* SNP in the population appeared the highest among a number of *SULT1A1* genotypes studied. For instance, it occurred at a frequency of about 0.30 in the Caucasians and about 0.17 in the Japanese population [77]. Additionally, *SULT1A1-R213H* SNP was found to be common among African American subjects (about 29%) [76]. Chinese populace presented with allelic frequencies of about 0.08 and 0.006 for *SULT1A1-R213H*, *SULT1A1*3* (M223V), respectively. Both of these two alleles presented with higher frequencies in African American subjects, 0.294 for *SULT1A1-R213H* and 0.229 for *SULT1A1*3* (M223V) [74, 76]. These differences in *SULT1A1* allele frequencies might contribute to the observed variability in drug disposition and metabolism among those different ethnic groups [72]. Due to the high frequency of *SULT1A1-R213H* SNP in the population and its potential effect on the bioconversion of different drugs and carcinogens, this variant has received much attention in genotyping studies [82].

A good number of molecular epidemiological studies has been carried out aiming to link *SULT1A1-R213H* polymorphism to disease susceptibility. An initial report suggested that the *SULT1A1-R213H* SNP is an independent risk factor for esophageal cancer in men [83]. Other studies suggested a positive correlation between *SULT1A1-R213H* allele and the risk of breast cancer [84], gastric cancer [85], as well as brain tumors [69]. Additionally, *SULT1A1-R213H* polymorphism has been shown to be a risk factor for lung cancer in different ethnicities/populations, including Caucasian [86], Turkish [87], and Bangladesh [88]. The exact mechanism underlying the risk for different cancers due to certain *SULT1A1* genotypes remains unclear [8, 9, 83, 89]. Contradictory results, however, also exist that indicated a lack of association between *SULT1A1* genotype and the risk for colorectal cancer [90] or prostate cancer [91] in Caucasian populations, as well as lung cancer [92] and urothelial epithelial cancers in a Japanese populace [93]. Moreover, in some other studies, *SULT1A1-R213H* SNP has been shown to be associated with a reduced incidence of bladder and colorectal cancers [82, 94]. It has been proposed that individual susceptibility to certain promutagenic and procarcinogenic compounds may ultimately be influenced by *SULT1A1* genetic polymorphisms [95].

### *SULT1A3/SULT1A3* SNPs and SULT1A3 allozymes

As noted above, *SULT1A3* and *SULT1A4* genes encode identical protein products, collectively designated SULT1A3 [16]. SULT1A3 is the major enzyme responsible for the sulfation of the catecholamines such as dopamine, epinephrine, and norepinephrine, as well as a number of drug and dietary compounds [5]. Unlike other SULTs, SULT1A3 is expressed only in humans and closely related primates [113]. In adult humans, SULT1A3 is expressed predominantly in the upper gastrointestinal tract, constituting nearly one-third of the total amount of SULTs present in the small intestine. In contrast, it has a very low level of expression in the liver [62,114]. Substantial expression of SULT1A3 is also found in the brain, lung, and platelets [56]. From the developmental standpoint, hepatic expression of SULT1A3 was found to be high at early stages of fetal development, but decreased substantially in late fetal/early neonatal liver, and essentially absent in adult liver. In the lung, significant SULT1A3 activity was observed in the fetus, whereas neonatal levels were considerably lower. In brain, low and widespread activity was recognized for SULT1A3 in different regions other than choroid plexus [64].

Earlier studies revealed a link between the *SULT1A* locus and the predisposition to autism spectrum disorders [115,116,117]. More recently, a correlation between autism and mutations in chromosome 16 at position 16p11.2, where the *SULT1A3 and SULT1A4* genes are located, was reported [118,119]. Furthermore, the sequences surrounding the *SULT1A3* and *SULT1A4* genes were found to be associated with several pathological disorders [120]. Individuals with microdeletions in these sequences were found to manifest high frequency of cognitive, developmental, and speech delay as well as behavior abnormalities [121] and autism spectrum disorders [117,122]. Moreover, duplications in the sequences surrounding the *SULT1A3 and SULT1A4* genes have been found to be associated with obesity [123], schizophrenia [124] and attention deficit hyperactivity disorder [125]. Genetic polymorphisms of both *SULT1A3* and *SULT1A4* have been studied. Initial studies revealed ethnic-specific inherited differences in the capacity of catecholamine sulfation [10,126]. In an earlier study, eleven *SULT1A3*/*SULT1A4* SNPs were identified and two of them, designated C302T, and C302A, were found to be cSNPs [16]. Corresponding SULT1A3 allozymes, expressed in COS-1 cells displayed lower enzymatic activity in comparison with the wild type enzyme, while without significant alterations in substrate kinetics [16]. In another study using DNA samples from 60 African-American (AA) and 60 Caucasian American (CA) subjects, eight single nucleotide polymorphisms (SNPs) were observed in AA and five in CA subjects, and a single amino acid change, Lys234Asn, has been shown to lead to accelerated SULT1A3 degradation [10]. In another study, four SULT1A3 allozymes (Lys234Asn, Pro101Leu, Pro101His and Arg144Cys) were found to display lower sulfating activity, compared with the wild-type enzyme, with ritodrine as a substrate [57].

More recently, the effects of *SULT1A3*/*SULT1A4* cSNPs on the sulfating activity of SULT1A3 allozymes were systematically investigated [127,128,129]. Twelve known SULT1A3 allozymes (SULT1A3-T7P, SULT1A3-S8P, SULT1A3-R9C, SULT1A3-P10L, SULT1A3-V15M, SULT1A3-V18F, SULT1A3-P101L, SULT1A3-P101H, SULT1A3-R144C, SULT1A3-K234N, SULT1A3-N235T and SULT1A3-S290T), bacterially expressed and purified, showed differential sulfating activity toward catecholamines and serotonin

as substrates. Interestingly, the variations in the sulfating activity of SULT1A3 allozymes toward dopamine were markedly smaller than those toward epinephrine, norepinephrine, and serotonin. Kinetic studies demonstrated differences in both substrate affinity and catalytic efficiency of the tested SULT1A3 allozymes. Of these allozymes, SULT1A3-N235T displayed the lowest sulfating activity and catalytic efficiency [127]. Several drugs including acetaminophen, morphine, tapentadol, *O*-desmethyltramadol, phenylephrine and salbutamol, were tested as substrates for these SULT1A3 allozymes [128,129]. The tested allozymes exhibited a similar pattern of differential sulfating activity toward these drugs, and kinetic studies showed further significant variations in their substrate-binding affinity and catalytic efficiency. The SULT1A3-N235T allozyme also exhibited the lowest sulfating activity toward the tested drugs. These findings may imply the differential pharmacokinetics and, consequently, efficacy and associated toxicity of these drugs when administered to individuals with distinct *SULT1A3* and *SULT1A4* genotypes [128,129].

### *SULT1B1* SNPs and SULT1B1 allozymes

Only a limited amount of information is available concerning the genetic polymorphism of *SULT1B1*. Studies have shown that certain *SULT1B1* SNPs may influence the activity of thyroid hormones and the mutagenicity of polycyclic aromatic hydrocarbons [130, 131]. Three nonsynonymous cSNPs (Leu145Val, Glu186Gly, and Glu204Asp) have been identified in human populations [132–134]. Among them, Leu145Val, with a 17% frequency in African American, had been shown to display a higher affinity toward 1-hydroxypyrenes than the wild-type enzyme [134]. No significant correlation between the *SULT1B1*variants and pathologies (colorectal or prostate cancers) associated with the subjects studied, however, was observed.

### *SULT1C2*/*SULT1C4* SNPs and SULT1C2/SULT1C4 allozymes

SNPs of *SULT1C2* and *SULT1C4* genes have been reported in human population [11,133]. For *SULT1C2*, 4 nonsynonymous cSNPs (encoding Asp60Ala, Arg73Gln, Ser111Phe, and Ser193Ala) have been identified in Caucasians [11]. Among the corresponding SULT1C2 allozymes, Asp60Ala and Arg73Gln showed reduced sulfating activity (15% of wild-type) toward *p*-nitrophenol and Ser111Phe showed no detectable activity [11]. Arg73Gln showed a much higher *Km* with PAPS, while Asp60Ala showed no change in *Km* with PAPS. These observations suggested that substitution of Arg73 with Gln may affect the interaction with PAPS. Since Ser111 is located in catalytic region that includes also the catalytic residue His109, substitution of Ser111 with Ala may alter the interaction of the enzyme with the substrate, *p*-nitrophenol. On the other hand, Ser193Ala showed no change in the catalytic properties. For *SULT1C4*, a nonsynonymous cSNP (encoding Asp5Glu) has been reported [133]. Although no information on the catalytic properties of the corresponding allozyme is available, Asp5Glu has been reported to correlate with a higher post-treatment relapse rate in acute myeloblastic leukemia [135]. Therefore, the clinical significance of the SNP will need to be clarified. It should be pointed out that polymorphisms of *SULT1C* subfamily may be particularly important in the fetal physiology vs. that of the adult in view of their more prominent expression at fetal stages [24,27].

### *SULT1E1* SNPs and SULT1E1 allozymes

SULT1E1 is known to be the most efficient SULT enzyme in catalyzing the sulfation of endogenous estrogens ($E_1$ and $E_2$), while with a lower efficiency in sulfating other hydroxysteroids (e.g., DHEA, pregnenolone), as well as some xenobiotics, including a number of drug compounds [13,32,39, 136–143]. SULT1E1 has been shown to be expressed in adult human lung, liver, and small intestine [62]. SULT1E1 expression has also been detected in other organs including breast, endometrium, adrenal gland, placenta, jejunum, lung, skin, and testis [32, 144–147], as well as human fetal kidney, liver, lung, thyroid gland, and choroid plexus [66].

Genetic variations of the *SULT1E1* gene have been found to be associated with the risk for certain cancers/disease etiologies, and responses to therapies [56,58]. In earlier studies, the *SULT1E1-64G/A* (rs3736599) genotype was found to be associated with a significant increase in the risk for developing endometrial tissue cancer [148], particularly in women receiving long-term hormone replacement therapy (HRT) [149]. A correlation between *SULT1E1-64G/A* (rs3736599) and catechol-*O*-methyl-transferase (COMT Val158Met), resulting in lower serum estradiol levels as well as increased risk for ischemic stroke, has also been reported [150]. Another study revealed that Korean women breast cancer patients with *SULT1E1 *959G>A* (rs3775778) and *SULT1E1 IVS4-1653 T>C* (rs3775775) base changes manifested a 4-fold increase in the risk for breast cancer [103]. Furthermore, a correlation between *SULT1E1 *959 G>A* (rs3775778) and reduced bone mineral density at the distal radius and calcaneus in healthy Korean women has been reported [151]. In another study, missense mutation (His224Gln) in SULT1E1 protein was implicated as a risk factor for breast cancer in Jewish women [152]. A more recent study revealed that two *SULT1E1* SNPs (*SULT1E1* rs1238574 and *SULT1E1* rs3822172) were associated with poor survival rate of colorectal cancer patients [153]. In a clinical study, three variants of the *SULT1E1* gene (*SULT1E1* -9-899G>A, *SULT1E1* -9-682A>G and *SULT1E1* -9-469A>G) were found to result in inter-individual variations of plasma concentrations of tamoxifen metabolites in breast cancer patients treated with tamoxifen, indicating contribution of SULT1E1 to tamoxifen metabolism *in vivo* [154]. Another clinical study showed a significant correlation between genetic variations of *SULT1E1* gene (*SULT1E1* rs3775777, *SULT1E1* rs4149534, *SULT1E1* rs10009305, *SULT1E1* rs3775770, *SULT1E1* rs4149527, and *SULT1E1* rs3775768) and the time to treatment failure (TTF) of abiraterone therapy in male patients with metastatic castration refractory prostate cancer [155]. The presence of one or more rare alleles among these six SNPs resulted in shorter TTF compared to those with wild-type alleles. These findings suggest that genetic variations of the *SULT1E* gene could potentially reduce the interval between abiraterone administration and its discontinuation due to different reasons including patient decision, cancer progression, adverse effects, and patient death.

Several studies on the effects of *SULT1E1* cSNPs on the functional activity of SULT1E1 protein product have been reported [12,156,157]. In an earlier functional genomic study, COS-1 cells transfected with constructs containing two nonsynonymous *SULT1E1* cSNPs (Ala32Val and Asp22Tyr) were found to exhibit reductions in both SULT1E1-sulfating activity toward $E_2$ (40% and 90%, respectively) as well as enzyme expression level

[12]. In a more recent study, five missense cSNPs of the *SULT1E1* gene (*SULT1E1*-A43D, *SULT1E1*-A131P, *SULT1E1*-R186L, *SULT1E1*-P214T, and *SULT1E1*-D220V) were bacterially expressed, purified, and characterized in regard to their sulfating activity toward endogenous estrogens ($E_1$, $E_2$, estriol ($E_3$)), EE2, 4-hydroxytamoxifen (4-OHT), and diethylstilbestrol (DES) [156,157]. Compared with the wild-type enzyme, all five SULT1E1 allozymes showed significant variations in the kinetics parameters ($V_{max}$, $K_m$, and $V_{max}/K_m$) toward $E_2$, 4-OHT and DES, reflecting the effect of these cSNPs on the sulfoconjugation of $E_2$, 4-OHT and DES by SULT1E1 allozymes [156]. With respect to the remaining substrates ($E_1$, $E_3$, and EE2), the sulfating activities of the five SULT1E1 allozymes were all significantly lower in comparison to the wild-type SULT1E1. The inhibitory effects of triclosan on $E_2$ sulfation by these SULT1E1 allozymes has also been evaluated [157]. In the presence of triclosan (150 μM), SULT1E1-A43D, SULT1E1-A131P, SULT1E1-R186L, and SULT1E1-D220V displayed 80%, 9%, 22%, and 70% decrease in $E_2$-sulfating activities, respectively, compared to the wild-type SULT1E1. These results demonstrated the significant inhibitory effect of triclosan on $E_2$ sulfation by SULT1E1 allozymes, indicating that exposure to triclosan may impact the endogenous estrogens hemostasis as well as the bioavailability of the compounds that are metabolized by SULT1E1. These results provide support for the notion that individuals with different *SULT1E1* genotypes may differ in biotransformation capacity in sulfating endogenous and exogenous estrogenic compounds as well as xenobiotics, suggesting inter-individual variations in susceptibility to certain diseases and responses to relevant therapies.

### *SULT2A1* SNPs and SULT2A1 allozymes

As noted above, SULT2A1 is known to display a strong activity toward DHEA and other hydroxysteroids, as well as a number of xenobiotic compounds including drugs [158–160]. Studies have demonstrated the expression of SULT2A1 at high levels in liver and intestine, as well as adrenal glands [161], and at low levels in the kidney and lung [161]. Being the primary enzyme responsible for the sulfation of DHEA, SULT2A1 plays an important role in the homeostasis of DHEA [162]. Effects of the variations of the *SULT2A1* gene on the sulfating activity of SULT2A1 or DHEA homeostasis have been studied. In an earlier study, a 4.6-fold variation in SULT2A1 enzymatic activity level was detected among 94 human hepatic tissue samples analyzed [163]. In a later study sequencing the *SULT2A1* gene in DNA samples from African-American and Caucasian-American individuals, a total of 15 SNPs were identified [164]. Three of these *SULT2A1* SNPs were non-synonymous cSNPs, with corresponding amino acid changes: Ala63Pro, Lys227Glu and Ala261Thr [164]. Intriguingly, these *SULT2A1* cSNPs were only detected in African-American individuals. The expression of SULT2A1 allozymes in COS-1 cells resulted in enzymes with varying levels of DHEA-sulfating activity when compared to wild-type SULT2A1 [164]. Another study conducted to analyze the *SULT2A1* gene in DNA samples from normal African-American men revealed the presence of two cSNPs, Ala63Pro and Ala261Thr, similar to those reported earlier [165]. Interestingly, a significant increase in the DHEA:DHEA-sulfate ratio was observed in individuals with a heterozygous G187C/G781A genotype that codes for the amino acid change Ala63Pro [165]. In a genome-wide association study of 14,846 individuals, a *SULT2A1* SNP (rs2637125) was identified as one of the eight common genetic variants linked to variations in serum DHEA-S levels [166].

In another study performed to investigate the association of *SULT2A1* SNPs with plasma DHEA-S concentration, it was found that both *SULT2A1* SNPs rs2637125 and rs182420 were associated with decreased levels of DHEA-S in 12-16 year old children [167]. In a more recent study, it was demonstrated that *SULT2A1* SNP rs182420 was associated with prostate cancer risk in Caucasians, while *SULT2A1* SNP rs2547238 was associated with prostate cancer risk in African-Americans [168]. Another epidemiological study revealed that *SULT2A1* SNP rs182420 was associated with a variation in DHEA-S levels in women with polycystic ovary syndrome [169]. Collectively, these studies indicated that *SULT2A1* SNPs have implications in the homeostasis of DHEA/DHEA-S as well as DHEA/sex hormone-associated diseases, including prostate cancer and polycystic ovary syndrome. In a study investigating the effects of *SULT2A1* SNPs, nine SULT2A1 allozymes, in comparison with the wild-type enzyme, were shown to display differential sulfating activities toward tibolone [170]. More recently, the functional consequences of a set of seven *SULT2A1* non-synonymous cSNPs were investigated [171,172]. The sulfating activities of these seven SULT2A1 allozymes were characterized with three kinds of substrates, those that carry hydroxyl group in their chemical structures, including DHEA, pregnenolone, tibolone, and budesonide, those that carry amine groups in their chemical structures, including ciprofloxacin and desipramine, and Δ4-3-ketosteroids, such as 4-androstene-3, 17-dione and progesterone, that do not carry hydroxyl or amine groups in their chemical structures. Results indicated that the seven SULT2A1 allozymes analyzed displayed differential sulfating activities toward all three types of substrates, compared with wild-type SULT2A1, reaffirming the impact of SULT2A1 SNPs on the functional activity of SULT2A1 protein products [172].

### *SULT2B1* SNPs and SULT2B1b allozymes

As noted above, two N-terminal variants, SULT2B1a and SULT2B1b, have been reported to be derived from the alternative splicing of the primary *SULT2B1* transcript [40,41]. Of the two, SULT2B1b has been reported to display a strong activity toward cholesterol, and thus dubbed a cholesterol sulfotransferase [173]. Additionally, SULT2B1b has also been shown to display activity toward hydroxysteroids, particularly 3β-hydroxysteroids including dehydroepiandrosterone (DHEA), pregnenolone, and androstenediol [174, 43]. Moreover, SULT2B1b can also sulfate oxygenated derivatives of cholesterol, collectively called “oxysterols”, such as 7-ketocholesterol (7KC), 5α,6α-epoxycholesterol (5α,6α-EC), 5β,6β-epoxycholesterol (5β,6β -EC), 25-hydroxycholesterol (25HC), and 24-hydroxycholesterol (24HC) [175–177]. Besides the endogenous substrates, SUlT2B1b has been reported to display sulfating activity toward xenobiotics, including a number of drug compounds, e.g., 3-OH-tibolone, raloxifene, bisphenol A, 4-n-octylphenol, 4-n-nonylphenol, diethylstilbestrol, 17-α-ethynylestradiol, and *p*-nitrophenol [174, 140, 39]. On the other hand, several antiandrogens including galeterone, abiraterone, cyproterone, and danazol have been reported to inhibit DHEA sulfation by SULT2B1b [136].

The ability of SULT2B1b to sulfate some important steroids and hydroxysteroids and its expression in many tissues/organs (including prostate, placenta, breast, endometrium, uterus, ovary, small intestine, colon, lung, platelet, brain, and skin), suggest the critical involvement of SULT2B1b in some physiological and pathological conditions in the human

body [178–183]. Indeed, reduction or elevation in SULT2B1b activity or expression level due to genetic variations have been linked to disease states like autosomal recessive ichthyosis and several types of cancers including prostate cancer, esophageal squamous cell carcinoma, hepatocellular carcinoma, gastric cancer, endometrial cancers, and colorectal cancer [184–192]. Several studies have been conducted to study the effect of *SULT2B1* genetic polymorphisms on the sulfating activity of the expressed enzyme [193–195]. The first such study revealed that of the samples taken from 120 African American and Caucasian subjects, four non-synonymous cSNPs (*SULT2B1b*-Leu51Ser, *SULT2B1b*-Asp191Asn, *SULT2B1b*-Arg230His, and *SULT2B1b*-Peo345Leu) were detected [193]. Corresponding SULT2B1b allozymes were transiently expressed in COS-1 cells and the sulfating activity was characterized using DHEA as a substrate [193]. Compared to wild-type SULT2B1b, the level of the tested allozymes in COS-1 cells varied from 79% to 112%, while their sulfating activity varied from 76% to 98% [193]. In a more recent study, the impact of ten *SULT2B1* non-synonymous cSNPs on the functional activity of corresponding SULT2B1b allozymes was investigated using cholesterol as a substrate [194]. Amino acid changes in three of the ten allozymes, SULT2B1b-Gly72Val, SULT2B1b-Arg147His, and SULT2B1b-Gly276Val, were found to result in a complete loss of the enzyme activity [194]. The other seven allozymes (SULT2B1b-Pro69Ala, SULT2B1b-Thr73Met, SULT2B1b-Asp191Asn, SULT2B1b-Arg230His, SULT2B1b-Ser244Thr, SULT2B1b-Arg274Gln, and SULT2B1b-Pro345Leu) all resulted in a dramatic decrease in the sulfating activity, substrate affinity, and catalytic efficiency [194]. Similar findings were later reported for these SUL2B1b allozymes using DHEA or pregnenolone as substrate [195]. Three allozymes (SULT2B1b-Gly72Val, SULT2B1b-Arg147His, and SULT2B1b-Gly276Val) exhibited no detectable sulfating activity toward DHEA or pregnenolone, whereas the other seven (SULT2B1b-Pro69Ala, SULT2B1b-Thr73Met, SULT2B1b-Asp191Asn, SULT2B1b-Arg230His, SULT2B1b-Ser244Thr, SULT2B1b-Arg274Gln, and SULT2B1b-Pro345Leu) displayed differential sulfating activity and affinity toward DHEA or pregnenolone [195]. Interestingly, only SULT2B1b-Pro69Ala and SULT2B1b-Arg274Gln showed a significant decrease in the co-substrate (PAPS) binding when tested using pregnenolone as the substrate [195]. Interestingly, among the ten SULT2B1 genotypes studied, *SULT2B1*-Arg274Gln heterozygous allele has been implicated in autosomal recessive ichthyosis (ARCI), previously reported to be associated with a reduced skin cholesterol-sulfating activity [189]. In a phenotype-genotype association study, two missense *SULT2B1* cSNPs (p. Arg100Trp and p. Glu78Lys) have also been implicated in a specific subtype of ARCI called congenital ichthyosiform erythroderma for which the underlying molecular mechanisms is yet to be clarified [190].

## 4. Concluding remarks

Despite that the biological sulfation has been known for well over a century, the research on the responsible enzymes had been slow until the 1980s. The past three decades have witnessed significant progress made in the elucidation of the diversity of the SULT enzymes and their enzymatic characteristics, the phylogenetic relationships between the SULTs, the structural biology of the SULTs, the developmental expression of the SULTs, and the mechanisms underlying the regulation of the *SULT* gene expression, as well as the

development of the zebrafish as a model for use in SULT research. While continued efforts need to be made in all these aspects of the SULT research, additional fronts, particularly the implications of the polymorphisms of the *SULT* genes and the systems biology regarding the physiological involvement of the SULTs - not only in the detoxification of xenobiotics but also in the homeostasis of key endogenous compounds such as thyroid/steroid hormones and catecholamine neurotransmitter/hormones - will need to be addressed.

## 5. Expert opinion

By virtue of their involvement in drug metabolism, drug-metabolizing enzymes play a crucial role in influencing the level of drugs *in vivo* [196]. With the advent of pharmacogenomics, mounting evidence has indicated that genetic variations of the genes coding for drug-metabolizing enzymes may lead to the differential metabolism and thus efficacy, as well as adverse drug reactions, of drugs in individuals with different genotypes. Variations in the genes coding for both Phase I enzymes, such as cytochrome P-450 2C9 [197] and 3A4 [198], and Phase II enzymes, such as COMT [199, 200] and N-acetyltransferase [201, 202], and UDP-glucuronosyltransferases [203, 204], have all been reported to significantly affect the efficacy and adverse effects of a variety of drugs. An important application of such information may lie in helping to formulate personalized drug regimens for individuals with unique drug-metabolizing enzyme genotypes. Compared with other Phase II enzymes, less is known concerning the impact of genetic variations of *SULT* genes on the metabolism of drugs that are metabolized, in part at least, by the coded SULT enzymes. A better understanding about how *SULT* SNPs may influence the drug-sulfating activity of SULT allozymes will similarly help understand the differential drug metabolism and aid in formulating personalized drug regimens. It should be reiterated that while nonsynonymous coding *SULT* SNPs have been shown to affect the drug-sulfating activities of resulting SULT allozymes, there is evidence that the stability and expression level of different SULT allozymes may also vary [8,10, 60,69]. More studies are warranted in order to fully elucidate the impact of *SULT* SNPs on the metabolism of relevant drugs.

In association with the role of *SULT* SNPs in influencing the efficacy of drugs are the associated adverse drug reactions. For example, doxorubicin, which has been reported to be metabolized by sulfation [205], is known to cause cardiotoxicity when used in the treatment of hematologic malignancies as well as solid and soft tumors [206,207]. Studies have shown that not all patients who received the same chemotherapeutic regimen developed cardiotoxicity, implying likely an underlying genetic predisposition [208,209]. The enzyme responsible for the sulfation of doxorubicin has been shown to be SULT1C4 [30]. It is an interesting question whether genetic polymorphisms of the *SULT1C4* gene may influence the doxorubicin-sulfating activity of SULT1C4 allozymes, thereby influencing the susceptibility to the development of cardiotoxicity in patients with different *SULT1C4* genotypes. Another example is the occurrence of idiosyncratic skin rash associated with the use of nevirapine (NVP) in the treatment of human immunodeficiency virus (HIV) infection [210,211]. Sulfation of 12-OH-NVP, a metabolite of NVP, has been proposed to be involved in this NVP-induced adverse drug reaction [212,213]. An interesting question is whether the genetic polymorphisms of the gene encoding SULT1A1, a major 12-OH-NVP-sulfating SULT [214] which is expressed in human skin cells [215,216], may influence the level

of 12-OH-NVP generated, thereby dictating the development of skin rash in patients with different *SULT1A1* genotypes.

Another area worthy of attention is the SULT-mediated sulfation of 3-nitrotyrosine and 3-chlorotyrosine as pertaining to intracellular oxidative/nitrative stress [217–219]. Studies have shown that 3-nitrotyrosine, generated via *de novo* nitration of tyrosine or degradation of tyrosine-nitrated proteins, can induce oxidative DNA damage [220] or trigger apoptosis in cultured cells [221], while 3-chlorotyrosine has been reported to increase free radical production and attenuate the intracellular NO synthase enzyme expression [222,223]. Studies have revealed SULT1A3 as the only SULT enzyme capable of sulfating 3-nitrotyrosine and 3-chlorotyrosine [217–219]. In view of the pathogenic effects of these latter compounds, it is an interesting question whether the genetic polymorphisms of the genes coding for SULT1A3, *SULT1A3* and *SULT1A4*, may dictate the differential sulfating activity of coded SULT1A3 allozymes, thereby influencing the capacity in mitigating the adverse effects of 3-nitrotyrosine and 3-chlorotyrosine generated under oxidative/nitrative stress conditions.

Finally, the effects of *SULT* genetic polymorphisms on the sulfation of endogenous compounds should not be overlooked. Several human SULTs, including SULT1A3, SULT1B1, SULT1E1, SULT2A1, SULT2B1a, and SULT2B1b (cf. Table 1), have been shown to be involved in the metabolism of key endogenous compounds such as catecholamine neurotransmitters and thyroid/steroid hormones. Anomalies in the metabolism of these endogenous compounds in individuals with certain *SULT* genotypes have been shown to lead to increased risk for cancers and other pathological conditions as elaborated above.

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## Abbreviations:

| | |
|---|---|
| **DHEA** | dehydroepiandrosterone |
| **PAPS** | 3’-phosphoadenosine 5’-phosphosulfate |
| **SULT** | cytosolic sulfotransferase |
| **SNP** | single nucleotide polymorphism |

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## Article highlights

- Cytosolic sulfotransferases (SULTs)-mediated sulfation is critically involved in the metabolism of key endogenous compounds such as catecholamines and steroid/thyroid hormones, as well as drugs and other xenobiotics.
- In humans, eighteen SULT genes, including five pseudogenes, have been identified and classified into five gene families.
- Like many other genes, single nucleotide polymorphisms (SNPs) occur for genes encoding the SULTs.
- Studies have shown that certain SULT genotypes may predispose risks for diseases.
- SULT allozymes, coded by distinct SULT genotypes, have been reported to display differential sulfating activities.
- Elucidation of the functional relevance of SULT SNPs may eventually aid in formulating personalized drug regimens and help develop strategies for mitigating anomalies in the metabolism of key endogenous compounds.

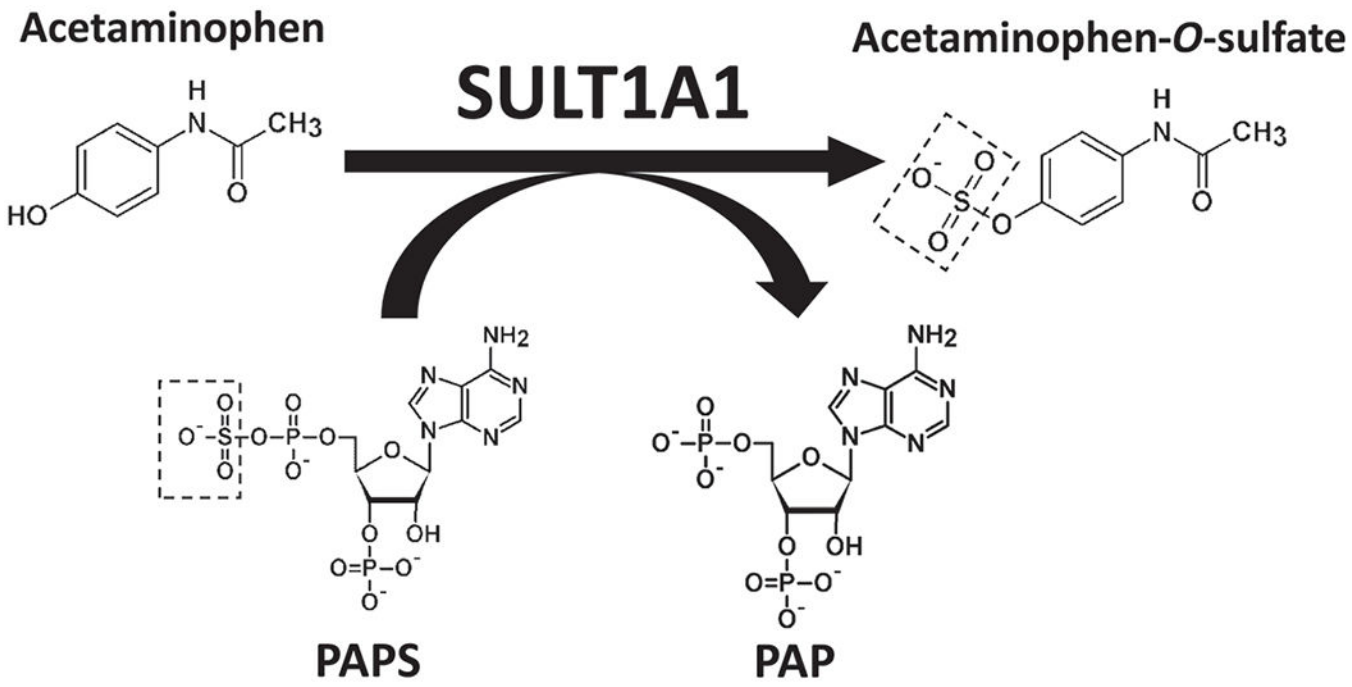


**Figure 1.**

SULT-mediated sulfation of acetaminophen. SULT1A1 catalyzes the transfer of the sulfonate (-$SO_3^-$) group from 3-phosphoadenosine-5'-phosphosulfate (PAPS), a co-substrate, to the hydroxyl (-OH) group of acetaminophen.

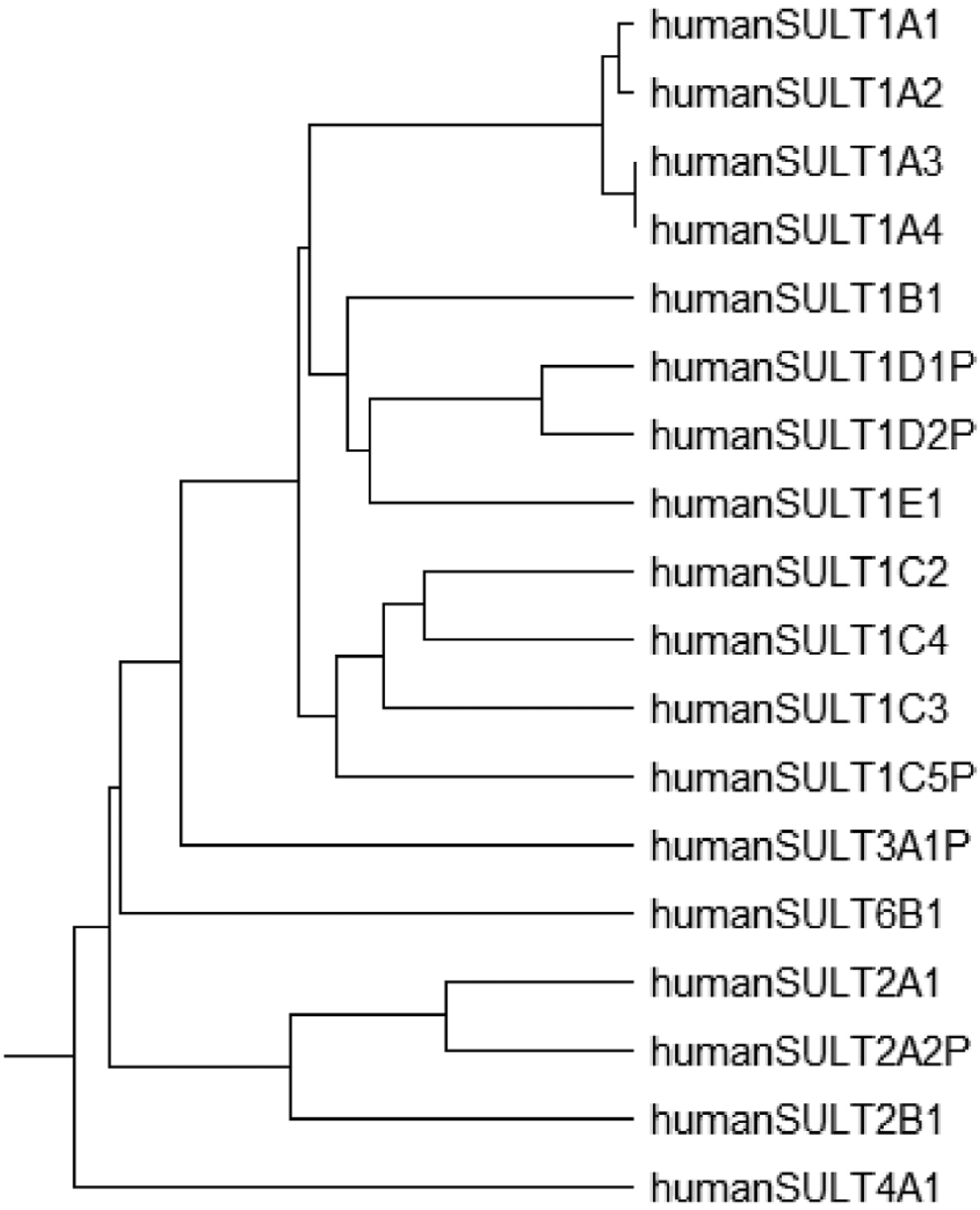


**Figure 2.**

Diagram illustrating the possible phylogenetic relationship between human SULT genes and pseudogenes. Phylogenic tree was prepared with CDS nucleotide sequences of SULT1A1 (NM_001055), SULT1A2 (NM_001054), SULT1A3 (NM_177552), SULT1A4(NM_001017390), SULT1B1 (NM_014465), SULT1C2 (NM_001056), SULT1C3a (NM_001320878), SULT1C4 (NM_006588), SULT1C5P(AK056906), SULT1D1P (NG_002642), SULT1D2P (NC_000003.12), SULT1E1 (NM_005420), SULT2A1 (NM_003167), SULT2A2P (), SULT2B1b (NM_177973), SULT3A1P

(NC_000014), SULT4A1 (NM_014351), SULT6A1 (NM_001367551). Hypothetical CDS nucleotide sequences of SULT1D1P were generated from the regions of exons 2 - 8 based on the NG_002642. For SULT1D2P, NC_000003.12, containing exons 2 - 8, was directly used as hypothetical CDS nucleotide sequences of SULT1D2P. For SULT1C5P, exons 2 - 7 were retrieved from AK056906 and NC_000002.12 using BLAST search as hypothetical CDS nucleotide sequences of SULT1C5P. For SULT2A2P, exons 2 - 3 were retrieved from NC_000019.10 using BLAST search as hypothetical CDS nucleotide sequences of SULT2A2P. For SULT3A1P, NC_000014, containing exons 2 - 7, was directly used as hypothetical CDS nucleotide sequences of SULT3A1P. Analysis of aligned sequence data was carried out in MEGA 11 ALPHA.

**Table 1.**

Human cytosolic sulfotransferases (SULTs) with their amino acid sequence length, gene location on chromosomes, substrate specificity and gene cloning timeline.

| SULT[1] | No. of AA[2] | Gene Location on Chromosome | Prototype Substrate | References |
|---|---|---|---|---|
| 1A1 | 295 | 16p12.1 | *p*-Nitrophenol | Wilborn et al., 1993; Dooley et al., 1994; |
| 1A2 | 295 | 16p12.1 | *p*-Nitrophenol | Zhu et al., 1996; Her et al., 1996 |
| 1A3 | 295 | 16p11.2 | Dopamine | Dooley et al., 1994; Aksoy and Weinshilboum, 1995 |
| 1B1 | 296 | 4q13.3 | Iodothyronines | Fujita et al., 1997 |
| 1C2 | 296 | 2q12.3 | *p*-Nitrophenol | Her et al., 1997; Sakakibara, 1998 |
| 1C3 | 304 | 2q12.3 | Bile acids; iodothyronines | Freimuth et al., 2000; Kurogi et al., 2017 |
| 1C4 | 302 | 2q12.3 | *p*-Nitrophenol | Freimuth et al., 2000; Sakakibara et al., 1998 |
| 1E1 | 294 | 4q13.1 | 17β-estradiol | Aksoy et al., 1994 |
| 2A1 | 285 | 19q13.3 | DHEA[1] | Otterness et al., 1992; Kong et al., 1992 |
| 2B1a | 350 | 19q13.3 | Pregnenolone | Her et al., 1998 |
| 2B1b | 365 | 19q13.3 | Cholesterol | Her et al., 1998 |
| 4A1 | 284 | 22q13 | unknown | Walther et al., 1999; Falany et al., 2000 |
| 6B1 | 265 | 2p22.3 | unknown | Freimuth et al., 2004 |

[1]Dehydroepiandrosterone

**Table 2.**

Summary of differential sulfating activities of human SULT allozymes toward endogenous hormones and drugs.

| SULT | Allozymes | Effects on the activities with hormones and drugs | References |
|---|---|---|---|
| 1A1 | Arg37Gln | acetaminophen (↓)*, *O*-desmethylnaproxen (↓)[2] | 78 |
| | Pro47Ser | acetaminophen (↓), *O*-desmethylnaproxen (↓) | 78 |
| | Met77Ile | acetaminophen (↑)** | 78 |
| | His149Tyr | acetaminophen (↓), *O*-desmethylnaproxen (↓) | 78 |
| | Tyr169Asp | acetaminophen (↓), *O*-desmethylnaproxen (↓) | 78 |
| | Arg213His | thyroxine (↓), acetaminophen (↓), *O*-desmethylnaproxen (↓) | 71, 78 |
| | Thr227Pro | acetaminophen (↓), tapentadol (↓) | 78 |
| | Val243Asp | acetaminophen (↓), *O*-desmethylnaproxen (↓) | 78 |
| | Fhe247Leu | acetaminophen (↑), *O*-desmethylnaproxen (↑) | 78 |
| 1A3 | Ser8Pro | *O*-desmethyltramadol (↓), salbutamol (↓) | 128, 129 |
| | Arg9Cys | norepinephrine (↓), serotonine (↓), acetaminophen (↓), morphine (↓), *O*-desmethyltramadol (↓) | 127, 128 |
| | Pro101Leu | ritodorine (↓), serotonine (↓) | 57, 127 |
| | Pro101His | ritodorine (↓) | 57 |
| | Arg144Cys | ritodorine (↓), serotonine (↓), acetaminophen (↓), phenylephrine (↓), | 57, 128, 129 |
| | Lys234Asn | ritodorine (↓) | 57 |
| | Asn235Thr | dopamine (↓), epinephrine (↓), norepinephrine (↓), acetaminophen (↓), morphine (↓), tapentadol (↓), *O*-desmethyltramadol (↓), phenylephrine (↓), salbutamol (↓) | 127, 128, 129 |
| 1E1 | Asp22Tyr | 17β-estradiol (↓) | 12 |
| | Ala34Val | 17β-estradiol (↓) | 12 |
| | Ala43Asp | estrone (↑), estriol (↑), 17β-estradiol (↓) 4-HO-tamoxifen (↓), diethylstilbestrol (↓) | 156, 157 |
| | Arg186Leu | 17β-estradiol (↓), 4-HO-tamoxifen (↓) | 156 |
| | Pro214Thr | 17β-estradiol (↓), diethylstilbestrol (↓) | 156 |
| | Asp220Val | 17β-estradiol (↓), 4-HO-tamoxifen (↓), diethylstilbestrol (↓) | 156 |
| 2A1 | | | |
| | Lys44Glu | 4-androstene-3, 17-dion (↓), progesterone (↓) tibolone (↓) | 172 |
| | Ala63Pro | DHEA (↓) | 164 |
| | Pro76Thr | DHEA (↓), pregnenolone (↓), 4-androstene-3, 17-dion (↓), progesterone (↓), tibolone (↓), budesonide (↓) | 171, 172 |
| | Glu147Lys | DHEA (↓), progesterone (↓), tibolone (↓) budesonide (↓) | 171, 172 |
| | Glu148Lys | DHEA (↓), pregnenolone (↓), 4-androstene-3, 17-dion (↓), progesterone (↓), tibolone (↓) budesonide (↓) | 171, 172 |
| | Leu159Val | DHEA (↑) | 170 |
| | Lys227Glu | DHEA (↓), tibolone (↓) | 164, 170 |
| | Leu246Pro | DHEA (↓), pregnenolone (↓), 4-androstene-3, 17-dion (↓), progesterone (↓), tibolone (↓), budesonide (↓) | 171, 172 |
| | Phe258Leu | DHEA (↓), pregnenolone (↓), 4-androstene-3, 17-dion (↓), progesterone (↓), tibolone (↓), budesonide (↓) | 171, 172 |
| | Gln262Glu | DHEA (↓) | 171 |
| 2B1 | Pro69Ala | DHEA (↓), pregnenolone (↓), cholesterol (↓) | 194, 195 |
| | Gly72Val | DHEA (↓), pregnenolone (↓), cholesterol (↓) | 194, 195 |

| SULT | Allozymes | Effects on the activities with hormones and drugs | References |
|---|---|---|---|
| | Thr73Met | DHEA (↓), pregnenolone (↓), cholesterol (↓) | 194, 195 |
| | Arg147His | DHEA (↓), pregnenolone (↓), cholesterol (↓) | 194, 195 |
| | Asp191Asn | DHEA (↓), cholesterol (↓) | 193, 194, 195 |
| | Arg230His | DHEA (↓), cholesterol (↓) | 193, 194, 195 |
| | Ser244Thr | DHEA (↓), pregnenolone (↓), cholesterol (↓) | 194, 195 |
| | Arg274Gln | DHEA (↓), pregnenolone (↓), cholesterol (↓) | 194, 195 |
| | Gly276Val | DHEA (↓), pregnenolone (↓), cholesterol (↓) | 194, 195 |
| | Pro345Leu | DHEA (↓), pregnenolone (↓), cholesterol (↓) | 194, 195 |

*(↓) refers to decreased activity toward the corresponding compounds.

**(↑) refers to increased activity toward the corresponding compounds.

**Table 3.**

Summary of potential diseases related to human *SULT* genetic polymorphisms.

| SULT | Polymorphism | Related diseases | References |
|---|---|---|---|
| 1A1 | Arg213His | brain tumor | 69 |
| | | breast cancer | 82, 84 |
| | | esophageal cancer | 83 |
| | | gastric cancer | 85 |
| | | lung cancer | 86, 87, 88 |
| | | colorectal cancer (reduced risk) | 82 |
| | | bladder cancer (reduced risk) | 94 |
| | | endometrial cancer | 148, 149 |
| | Met223Val | endometrial cancer | 149 |
| | 3'-UTR variant (rs6839, rs1042157) | endometrial cancer | 148 |
| 1A3 | low copy number | alzheimer's disease | 120 |
| | chromosomal mutation in *SULT1A3/SULT1A4* gene area (16p11.2) * | autism | 115–119, 121, 122 |
| | | obesity | 123 |
| | | schizophrenia | 124 |
| | | attention deficit hyperactivity disorder | 125 |
| 1C4 | Asp5Glu | higher post-treatment relapse rate in acute myeloblastic leukemia | 133 |
| 1E1 | His224Gln | breast cancer | 152 |
| | 5'-UTR variant (rs3736599) | endometrial cancer | 148, 149 |
| | | ischemic stroke in young adults | 150 |
| | intron variant (rs3775778) | breast cancer | 103 |
| | | reduced bone mineral density | 151 |
| | intron variant (rs3775775) | breast cancer | 103 |
| | intron variant (rs1238574) | poor survival rate of colorectal cancer | 153 |
| | intron variant (rs3822172) | poor survival rate of colorectal cancer | 153 |
| 2A1 | intron variant (rs182420) | prostate cancer, polycystic ovary syndrome | 168, 169 |
| | intron variant (rs2547238) | prostate cancer | 168 |
| 2B1 | Arg274Gln | autosomal recessive ichthyosis | 189 |
| | Arg100Trp | congenital ichthyosiform erythroderma | 190 |
| | Glu78Lys | congenital ichthyosiform erythroderma | 190 |
| | intron variant (rs4149455) | esophageal squamous cell carcinoma | 191 |
| | intron variant (rs3760806) | colorectal cancer | 153 |
| 4A1 | 5'-UTR variant (D22s1749e) | schizophrenia | 48 |
| | intron variant (rs138060) | schizophrenia | 49 |
| | intron variant (rs138097) | schizophrenia | 49 |

* These mutations (deletion and duplication) occur in the 16p11.2 at which *SULT1A3/SULT1A4* genes are located in. No potential SULT allozymes have been identified in these studies.