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PHARMACOGENETICS OF SULFOTRANSFERASE

K. Nagata and Y. Yamazoe
Division of Drug Metabolism and Molecular Toxicology, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980–8578, Japan; e-mail: nagataki@mail.pharm.tohoku.ac.jp

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■ **Abstract** Cytosolic sulfotransferase catalyzes sulfoconjugation of relatively small lipophilic endobiotics and xenobiotics. At least 44 cytosolic sulfotransferases have been identified from mammals, and based on their amino acid sequences, these forms are shown to constitute five different families. In humans, 10 sulfotransferase genes have been identified and shown to localize on at least five different chromosomes. The enzymatic properties characterized in the recombinant forms indicate the association of their substrate specificity with metabolisms of such nonpeptide hormones as estrogen, corticoid, and thyroxine, although most forms are also active on the sulfation of various xenobiotics. Genetic polymorphisms are observed on such human sulfotransferases as ST1A2, ST1A3, and ST2A3.

INTRODUCTION

Cytosolic sulfotransferase (SULT) plays an important role in the detoxication and activation of endogenous and exogenous compounds (1–4). The reaction catalyzed by this enzyme involves transfer of a sulfonate group from 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to the acceptor substrate to form either a sulfate or sulfamate conjugate (1, 2). Considerable numbers of cytosolic SULTs have been characterized at the mRNA level and divided into several gene families based on the similarity of their amino acid sequences and catalytic properties in mammals (5, 6). An international sulfotransferase nomenclature workshop suggested using ''SULT'' as the abbreviation for these enzymes and their genes. The names of individual forms, however, have not been universally agreed upon. In this context, a nomenclature system for SULTs is suggested here as a result of a comparison of currently characterized forms of mammalian SULTs.

The pharmacogenetics of drug sulfation by human platelets are known (7–9). Human platelet phenol SULT activity differs widely among individuals (8, 10) and now has been characterized by genotype using recent advanced molecular techniques (11–14). Current understanding of pharmacogenetics of human SULT is also summarized here.

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SULT GENE

A nomenclature for the SULT gene family is not yet in common use, although ''SULT'' has been agreed upon to be used as the acronym. In fact, some groups use SULT1A1 for one of human phenol SULTs (12) and others for rat phenol sulfotransferase (PST) (15). A similar phenomenon is observed for other SULTs (15–17). As a result, the name SULT has become very confusing. Recent pharmacogenetic studies have revealed several alleles of SULT genes through discovery of mutations (11–14), and there is a need to use a universal nomenclature. Here, a nomenclature system that is based on the cytochrome P450 nomenclature system is shown (18, 19). Known mammalian SULT cDNA sequences are compared and listed in Table 1. Basically, SULTs in one gene family have less than 40% similarity to SULTs in other gene families. Within a gene family, any SULTs in one subfamily have 40–65% similarity to SULTs in any of the other subfamilies. Numbers in parentheses indicate the accession number obtained from the Entrez Protein database, which links with the accession number of the nucleotide database. Using an unweighted-pair-group method of analysis, we have made a dendrogram (Figure 1). The family and subfamily are classified based on homology. Individual numbers of families and forms are termed as sequential chronological numbers.

The first enzyme characterized at the cDNA level among all SULTs is bovine estrogen SULT (20), which was named ST1E1 for the first family and estrogen SULT. Rat phenol SULT was called ST1A1 because it was the first cDNA isolated in the SULT1A subfamily (21). We believe that this method, based on cDNA information, is better than the method based on the currently known human gene. The reasons are as follows: (a) We still don't know how many SULT genes exist in humans as well as in experimental animals. Partial sequences likely to correspond to unknown SULTs are found in the expression tag sequence (EST) database. (b) A gene referred to as orthologous in two species is driven from the ancestral gene that existed before the evolutionary divergence of the two species. For example, only one form of SULT1B was identified from rat, human, and mouse as ST1B1, ST1B2, and St1b3, respectively (17, 22–24). The three forms show 72–88% homology and preferentially catalyze the sulfation of thyroid hormone. These results suggest that these three genes may be orthologous. However, a number of species-specific gene duplications and gene-conversion events have been shown in several subfamilies of cytochrome P450 (18). In fact, highly similar SULT genes have also been found in human SULT1A and rat SULT2A subfamilies (6, 25). Therefore, a new gene of human SULT including the SULT1B subfamily could possibly be found in the future. The current information is still too primitive to verify this possibility at the gene level at the present time (18).

TABLE 1 Correspondences of cytosolic SULTs and GenBank accession numbers

ST1A1 rat (X52883) (21)	PST-1 (X52883) (21), Mx-STb (L19998) (68), ASTIV (X68640) (69), Tyrosine-ester (U323721)
ST1A2 human (X78282) (70)	SULT1A2 (NM_001054) (46), HAST4V (U28169) (71), HAST4 (U28170) (71), STP2 (U33886) (53)
ST1A3 human (X78283) (70)	SULT1A1 (NM_001055, AJ007418) (46), (72), HAST1, Hpsta (L10819) (73), TS PST1 (U52852) (72), HAST2 (U09031, L19955) (74), P-PST (L19999) (75), STP (X84654, U54701) (76), (44), H-PST (U26309) (77)
St1a4 mouse	mST_{p1} (L02331) (78)
ST1A5 human	SULT1A3, hTLPST (U20499) (79), HAST3 (L19956) (74), TL PST (U08032) (79), hEST (L25275) (80), STM (X84653, U37686) (76), (55), HAST5 (U34199)
ST1A6 bovine	PST (L33828, U35253) (81)
ST1A7 dog	dPST-1 (D29807)
ST1A8 rabbit (AB029494)	
ST1A9 monkey	monPST-1 (D85514)
ST1B1 rat (D89375) (23)	dopa/tyrosine SULT (U38419) (22)
ST1B2 human (D89479) (23)	hST1B2 (U95726) (24)
St1b3 mouse	mouse SULT1B1 (AF022894) (17)
ST1C1 rat (L22339) (29)	HAST-1 (L22339) (29)
ST1C2 human (AB008164) (30)	human SULT1C SULT 1 (AF026303) (31) human SULT1C1 (NM_001056) (32)
ST1C3 human	human SULT1C SULT 2 (AF055584) (31)
St1c4 mouse	P-ST (AF033653) (33)
ST1C5 rabbit	Stomach SULT (AF026304)
ST1C6 rat	sultK1 (AJ238391)
ST1C7 rat	sultK2 (AJ238392)
St1d1 mouse	SULT-N (AF026073) (34)
ST1D2 rat	tyrosine-ester SULT (U32372)
ST1E1 bovine	OST (X56395) (20)
ST1E2 rat	EST-1, Ste 1 (U50204), EST-3 (M86758, S76489) (36), (37)
ST1E3 guinea pig	EST (U09552) (82)
ST1E4 human	hEST (L25275, U08098, Y11195) (80), (83), hEST-1 (S77383) (61)
St1e5 mouse	testis-specific estrogen SULT (S78182) (84)

(continued)

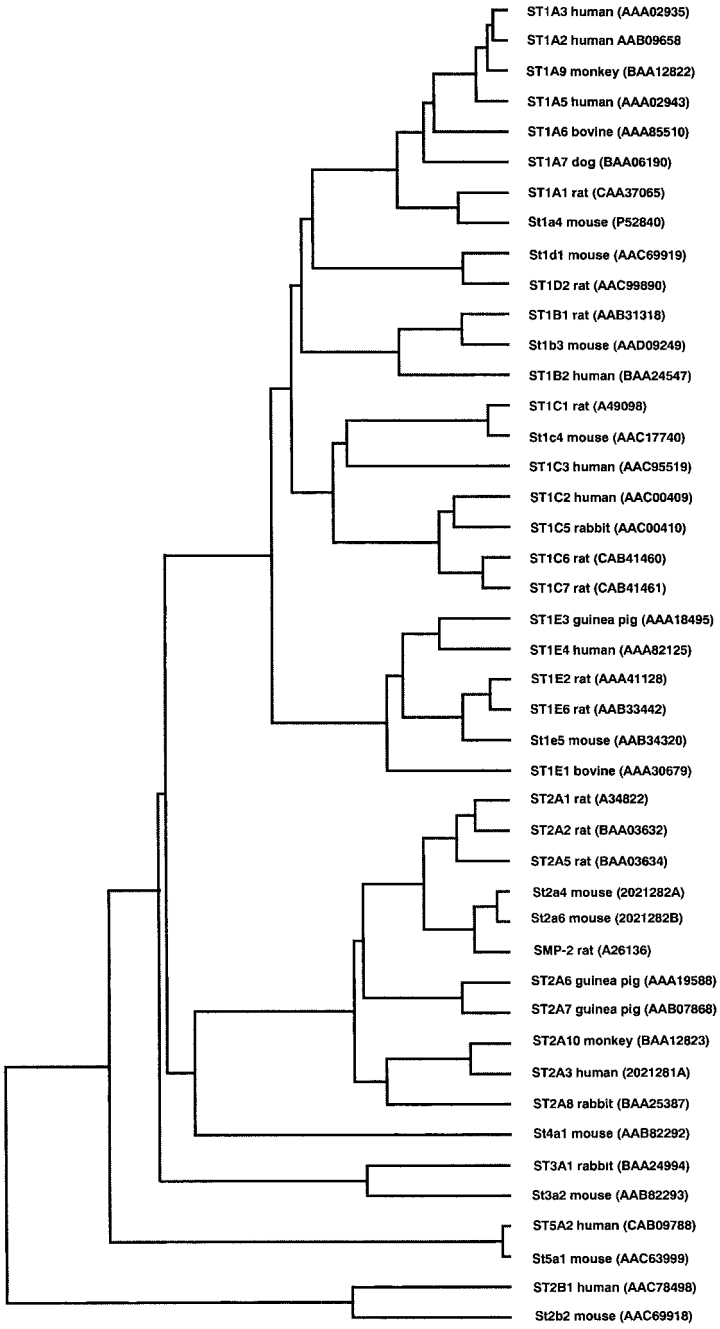
TABLE 1 *Continued*

ST1E6 rat	EST-2, Ste2 (U50205) (85), EST-6 (S76490) (37)
ST2A1 rat (M31363) (39)	ST-20 (M31363) (39), ST-21a (D14987) (25), ST-21b (D14988) (25)
ST2A2 rat (M33329) (86)	ST-40 (M33329) (86), ST-41 (X63410) (40)
ST2A3 human	DHEA-SULT (U08025) (87), HST-hfa (U08024) (88), hSTa (S43859) (89), DHEA-ST8 (L20000) (90)
St2a4 mouse	mST_{a1} (L02335) (91)
ST2A5 rat	ST-60 (D14989) (25)
ST2A6 guinea pig	gpHST1 (U06871) (63)
ST2A7 guinea pig	gp HST2 (U&35115) (92), Preg-ST (U55944) (93)
ST2A8 rabbit (AB006053) (64)	AST-RB2 (AB006053) (64),
St2a9 mouse	mST_{a2} (L27121) (94)
ST2A10 monkey	monHST-1 (D85521)
ST2B1 human	SULT2B1a (U92314) (16), SULT2B1b (U92315) (16)
St2b2 mouse	mouse SULT2B1 (AF026072) (34)
ST3A1 rabbit (D86219) (27)	AST-RB1 (D86219) (27)
St3a2 mouse	SULT-X2 (AF026075)

CLASSIFICATION

Mammalian SULTs have been classified into two groups (SULT1 and SULT2 families) based on their similarity of amino acid sequences and enzymatic properties. Enzymes included in SULT1 and SULT2 families transfer sulfonate to hydroxy groups of phenols and alcohols, respectively (5, 6, 26). A SULT catalyzing the formation of a sulfamate has recently been isolated from rabbits (27). This form constitutes a third gene family of SULT (SULT3). In addition, unique SULT cDNAs consisting of two new families (SULT4 and SULT5) are found in the DNA database, although properties of enzymes encoded by these SULT cDNAs have not yet been characterized. As shown in Figure 1, mammalian SULTs are classified into five families that share less than 40% similarity with

Figure 1 The classification of cytosolic SULTs previously reported based on their primary amino acid sequences. This dendrogram was made with the GeneWorks program (Intelli Genetics). The nomenclature was modified from that proposed by Y Yamazoe et al (5). The classification was performed according to the nomenclature system for the cytochrome gene superfamily. Any SULT in one gene family has $<$ 40% similarity to a SULT including other gene families. Within a gene family, any SULT in one subfamily is 40–65% similar to a SULT in any of the other subfamilies. Figures in parentheses represent the accession number in the protein database, which links to the nucleotide database.


ST1A3 human (AAA02935)
ST1A2 human AAB09658
ST1A9 monkey (BAA12822)
ST1A5 human (AAA02943)
ST1A6 bovine (AAA85510)
ST1A7 dog (BAA06190)
ST1A1 rat (CAA37065)
St1a4 mouse (P52840)
St1d1 mouse (AAC69919)
ST1D2 rat (AAC99890)
ST1B1 rat (AAB31318)
St1b3 mouse (AAD09249)
ST1B2 human (BAA24547)
ST1C1 rat (A49098)
St1c4 mouse (AAC17740)
ST1C3 human (AAC95519)
ST1C2 human (AAC00409)
ST1C5 rabbit (AAC00410)
ST1C6 rat (CAB41460)
ST1C7 rat (CAB41461)
ST1E3 guinea pig (AAA18495)
ST1E4 human (AAA82125)
ST1E2 rat (AAA41128)
ST1E6 rat (AAB33442)
St1e5 mouse (AAB34320)
ST1E1 bovine (AAA30679)
ST2A1 rat (A34822)
ST2A2 rat (BAA03632)
ST2A5 rat (BAA03634)
St2a4 mouse (2021282A)
St2a6 mouse (2021282B)
SMP-2 rat (A26136)
ST2A6 guinea pig (AAA19588)
ST2A7 guinea pig (AAB07868)
ST2A10 monkey (BAA12823)
ST2A3 human (2021281A)
ST2A8 rabbit (BAA25387)
St4a1 mouse (AAB82292)
ST3A1 rabbit (BAA24994)
St3a2 mouse (AAB82293)
ST5A2 human (CAB09788)
St5a1 mouse (AAC63999)
ST2B1 human (AAC78498)
St2b2 mouse (AAC69918)

each other. SULT1 has the largest number of enzymes and is further divided into five subfamilies (SULT1A, SULT1B, SULT1C, SULT1D, and SULT1E). The SULT2 family is separated into two subfamilies (SULT2A and SULT2B).

At least nine SULT1A forms, from experimental animals and humans, are members of the SULT1A subfamily (Figure 1), but the properties of monkey, mouse, and rabbit SULT1A forms have not yet been determined. The ST1A forms, except for human ST1A5, commonly catalyze sulfations of ρ-nitrophenol and α-naphthol. ST1A5 catalyzes the sulfation of dopamine, although a limited activity for ρ-nitrophenol is observed (28).

ST1B1 and ST1B2 were isolated as a thyroid hormone SULT from rats and humans, respectively (22–24). Mouse St1b3 is also shown to have an activity for thyroid hormone (17). Therefore, this SULT family seems to have a thyroid hormone-sulfating activity as a common catalytic property.

ST1C1, which mediated the activation of N-hydroxy-2-acetylaminofluorene (N-OH-AAF) through sulfate formation, was first isolated from rats (29). Other members of this subfamily include ST1C2 and ST1C3 from human (30–32), St1c4 from mouse, ST1C5 from rabbit, and ST1C6 and ST1C7 from rat. Mouse St1c4, which is reported as an olfactory-specific form (33), shares a high extent of homology (94%) with ST1C1, but human ST1C2 and ST1C3, and rabbit CT1C5, show lower extents of homology with ST1C1. ST1C2, ST1C3, and St1c4 have been reported to catalyze the sulfation of N-OH-AAF, although ST1C2 did not mediate DNA binding of N-OH-AAF in our experiment (30).

SULT1D was recently identified as St1d1 from the mouse (34). This form catalyzes the sulfation of serotonin and ecosanoids as well as ρ-nitrophenol and dopamine (35). Isolation of rat ST1D2 is also reported.

Six forms of SULT1E have been identified from bovine, rat, mouse, guinea pig, and human. These forms show a high affinity for sulfation of estrogen. Bovine ST1E1 is the first form whose primary structure has been characterized at a molecular level (20). A single form is found in each experimental animal species except for rats. Two SULT1E forms, ST1E2 and ST1E6, have been isolated from rats (36, 37). The three-dimensional structure of mouse St1e4 has been determined from X-ray data analysis of the crystallized PAPS-bound form (38).

The sulfation of alcohols is mainly catalyzed by forms of the SULT2 family (SULT2A and SULT2B subfamilies). At least four different cDNAs of SULT2A forms (ST2A1, ST2A2, ST2A5, and SMP-2) have been reported in rats (25, 39–41). SMP-2 was at first reported as a senescence marker protein and later found to have a high homology to the SULT2A form (41). The mRNA and gene corresponding to SMP-2 have not been confirmed, and thus the existence of the gene exactly related to SMP-2 in rat is doubtful. SULT2B forms were isolated from human (ST2B1) and mouse (St2b2) through the EST database (16). SULT2B forms as well as SULT2A forms prefer dehydroepiandrostene as the substrate. Judging from the dendrogram shown in Figure 1, ST2B forms seemed to diverge early from an ancestral SULT to constitute an independent family. Human SULT2B1a and ST2B1b are composed of 350 and 365 amino acids, which are

53 and 68 amino acids longer than SULT2A3, respectively. Alignment of ST2A3 and ST2B1 forms showed 48% homology at the protein level, indicating that ST2A and ST2B forms are members of the same family.

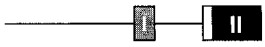
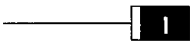
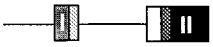
A novel SULT (ST3A1) has been isolated from rabbit livers in the authors' laboratory (27). ST3A1 represents the third gene family, SULT3, and shows a selectivity for the conversion of amino compounds to sulfamates (42). An enzyme related to ST3A1 is not detected in human and rat livers by Western and Northern blotting procedures. A nucleotide sequence similar to that of ST3A1 was found in the mouse GenBank database, although the properties of the protein encoded by the cDNA have not been reported. Three nucleotide sequences related to SULT, which are not classified into the three known families described above, are found in the nucleotide database. Based on their deduced amino acid sequences, these genes are judged to consist of new families of SULT, SULT4 and SULT5. We arbitrarily termed them St4a1, St5a1, and ST5A2, respectively. Mouse St4a1 and St5a1 cDNAs are identified from mouse kidney and brain, respectively. ST5A2 is identified in human chromosome 22.

REGULATION OF SULT GENE EXPRESSION IN HUMAN

Plural types of cDNA for each human SULT are registered in the DNA database except for ST1E4 and ST2A3. These differences are confined to the 5'-untranslated region (UTR) and are thus attributed to the existence of alternative sites for transcription initiation (6). Until now, three different ST1A2 cDNAs, four ST1A3 cDNAs, and five ST1A5 cDNAs have been isolated from different human tissues, as shown in Figure 2. Human SULT genes, except for ST1B2, ST1C2, and ST1C3, have been isolated and the structures determined (43–47). The open reading flames of SULT1 and SULT2 families consist of 7 and 6 exons, respectively. A single exon 1 for ST1E4, two exon 1s (exon 1a and exon 1b) for ST1A2 and ST1A3, and three exon 1s (exon 1a, exon 1b, and exon 1c) for ST1A5 are identified by their genes and mRNAs, but these exons do not contain coding regions of their proteins (6). On the other hand, exon 1 for ST2A3 and ST2B1 encodes the N terminus (16, 43). Therefore, the variety of the 5'-UTR sequences for these SULTs is generated by alternative transcription initiation, alternative splicing, or both mechanisms. The expression of some SULTs is known to be regulated by hormones (48–50). However, the molecular mechanism of SULT gene expression has not been well characterized.

SULT1A

Three SULT1A forms have been identified in humans, as shown in Table 1. Classical pharmacogenetic studies of the human sulfation have been done to determine the substrate specificity, inhibitor sensitivity, or thermal stability (7–9).

Gene name	Gene structure	cDNA	Accession number	Tissue
			(U34804)	Liver
ST1A2			R09752*	Fetal liver/spleen
(U34804, U71086, U76619)			U28169	Liver
			U28170	Liver
			L19955	Brain
			U26309	Hipppocampus
			U09031	Brain
			(U52852)	Liver
ST1A3			(U52852)	Liver
(AH003659, U37025, U52852)			L19999	Liver
			L10819	Liver
			X84654	Platelet
			X78283	Liver
			H67938*	Fetal liver/spleen
			AA325280*	Cerebellum
			W76361*	Fetal heart
			W81033*	Fetal heart
ST1A5			L25275	Placenta
(U20499, U37686)			L19956	Brain
			U20499	Liver
				Brain
			U08098	Liver
			AR003684	Unknown
			Y11195	Embryo
ST1E4			AA460624*	Total fetus
(AH006624)			AA448993*	Total fetus
			N83541*	Fetal heart
			AA334071*	Embryo
			L02337	Liver
			X84816	Fetus
			U08025	Liver
			T74488*	Liver
ST2A3			L20000	Liver
			U08024	Liver
(AH003200, AH006684)			T68221*	Liver
			Z21023*	Liver
			AA328456*	Embryo
		2B1a 	U92314	Placenta
ST2B1		2B1b 	U92315	Placenta
(AH007006)				

SULTs catalyzing phenol sulfations are referred to as thermostable (TS)/phenol-preferring (P) PST and the thermolabile (TL)/monoamine-preferring (M) PST (8, 51). Two genes (ST1A2 and ST1A3) of TS PST have been identified and localized to chromosome 16p12.1–11.2 (46, 52, 53). ST1A2 is located in the approximately 45-kb distant region of ST1A3. ST1A2 and ST1A3 catalyze the sulfation of ρ-nitrophenol and the activation of heterocyclic amines. These forms are sensitive to 2,6-dichloro-4-nitrophenol, a typical inhibitor of SULT (28). ST1A3 shows higher catalytic activity and lower Km value for ρ-nitrophenol than does ST1A2 (28). A gene (ST1A5) corresponding to TL PST has been isolated and localized to chromosome 16p11.2 (54, 55). ST1A5 is mapped at about 100 kb from ST1A2 and ST1A3 (56).

Studies on individual variations of TS PST indicate that phenotypic variations in both platelet TS PST activity and thermal stability are associated with ST1A3 polymorphism (57). Four allelic variants accompanying amino acid exchange in ST1A3 have been identified (11, 12, 14). One of them, ST1A3*2, is associated with both low TS PST activity and low thermal stability. The ST1A3*2 allele has a G→T mutation at ST1A3 cDNA nucleotide 638 located in exon 7, resulting in an Arg 213→His change in amino acid (Table 2). The allele frequency of ST1A3*2 is reported to be 0.31 to 0.37 in Caucasians and Nigerians, as shown in Table 2. The frequencies of two other alleles are quite lower than that of ST1A3*2 and reported to be 0.01 and 0.003 for ST1A3*3 and ST1A3*4, respectively. A genetic polymorphism accompanying amino acid exchange in ST1A2 is also found with the frequency of 0.38 (ST1A2*2). The frequencies of the haplotypes ST1A2*1/ ST1A3*1 and ST1A2*2/ST1A3*2 are highly similar to allele frequencies of ST1A2*1 and ST1A2*2 or ST1A3*1 and ST1A3*2. These data suggest that ST1A2*2 and ST1A3*2 alleles are associated (58).

SULT1B

Human SULT1B (ST1B2) has been identified (23, 24). This form catalyzes sulfation of 3, 3', 5'-triiodothyronine and ρ-nitrophenol (28), although both sulfations are also catalyzed by other SULTs, including the SULT1 family (28). A recent study on their enzyme kinetics and expressions showed that 3, 3', 5'-triiodothyronine and ρ-nitrophenol are preferentially sulfated by ST1B2 and ST1A3, respectively, in human livers (28). Similar results were also obtained with rat ST1B1 (59). Kinetic parameters for PAPS and 3, 3', 5'-triiodothyronine are quite similar between ST1B2 and ST1B1. Chromosome localization and genetic

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Figure 2 Structure of human SULT cDNA 5'-untranslated region. Gene structures are shown in only the first and second exons of individual genes. The figures in parentheses represent the accession numbers for SULT genes, and the asterisks represent the accession numbers for EST.

TABLE 2 Chromosomal localization and allele frequency of human SULTs

Chromosomal localization	Genotype	Substitution		Allele frequency
		Nucleotide	Amino acid	
16p12.1-p11.2	*ST1A2*1*			
	*ST1A2*2*	T20C, A706C	Ile7Thr, Asn235Thr	0.38
16p12.1-p11.2	*ST1A3*1*			
	*ST1A3*2*	G638A	Arg213His	0.31-0.37
	*ST1A3*3*	A667G	Met223Val	0.01
	*ST1A3*4*	G110A	Arg37Gln	0.003
16p11.2	*ST1A5*	–	–	–
–	*ST1B2*	–	–	–
2q11.1-q11.2	*ST1C2*	–	–	–
–	*ST1C3*	–	–	–
4q13.1	*ST1E4*	–	–	–
19q13.3	*ST2A3*1*			
	*ST2A3*2*	T170C	Met57Thr	0.027
	*ST2A3*3*	A557T	Glu186Val	0.038
19q13.3	*ST2B1*	–	–	–
22	*ST5A2*	–	–	–

polymorphism are still unknown, although a wide individual variation in the hepatic level of ST1B2 in human livers is observed (28).

SULT1C

SULT1C was first isolated from rat as an N-hydroxy-2-acetylaminofluorene (N-OH-AAF) SULT (ST1C1) (29). Two human SULT1C cDNAs (ST1C2 and ST1C3) have been identified through the EST database (30–32). Both amino acid sequences deduced from the nucleotide sequences shared about 63% identity with that of ST1C1. These human ST1C2 and ST1C3 shared 62.9% identity in their amino acid sequences with each other, which suggests that these three genes may have diverged from the same ancestor at an earlier era than when primates and rodents diverged. ST1C2 mRNA is expressed in adult human stomach, kidney, and thyroid, as well as in fetal kidney and liver (32). ST1C3 mRNA is expressed at higher levels in fetal lung and kidney and at lower levels in fetal heart, adult kidney, ovary, and spinal cord (31). An ST1C gene sharing a higher homology with ST1C1 was identified from humans (60). The amino acid sequence deduced from exon 7 and exon 8 showed 85.6% identity with that of ST1C1, although the

expression has not been identified in human. The chromosome localization is reported to be on chromosome 2q11.1-q11.2 for ST1C2 (32).

SULT1E

A gene of human SULT1E (ST1E4) has been identified and located on chromosome 4q13.1 (45). ST1E4 is a typical estrogen sulfotransferase (28, 61). The Km value for β-estradiol is lowest (0.25 μM) among human SULTs (28). The hepatic level of ST1E4 in human is correlated with the sulfation activity of β-estradiol ($r = 0.88$). The level of ST1A3 is, however, also correlated with the sulfation activity of β-estradiol ($r = 0.90$) (28), when the activity is determined at 0.5 μM of the substrate concentration. These phenomena might be explained by differences in expressed levels of both forms in the tissue: In human livers, the ST1A3 level is nine times higher than that of ST1E4 (28). The plasma level of β-estradiol is known to be around 0.5 nM. These data thus suggest that estrogen sulfation is the main physiological role of ST1E4 in humans, although the pharmacological or physiological role of ST1A3 is not excluded. Although the expression level of ST1E4 varies among individuals, the genetic polymorphism has not been reported (28).

SULT2A

Plural SULT2A forms have been isolated from a rodent species and display different substrate specificity on the sulfation of hydroxysteroids (62–64). However, the single form, ST2A3, is contained in humans and catalyzes the sulfation of hydroxysteroids, including bile acids (43). ST2A3 is highly expressed in human adrenals and livers (47). Liver ST2A3 activity has been shown to vary more than fivefold and has shown bimodal distribution when approximately 25% of subjects were included in a high-activity subgroup (65). ST2A3 consists of 6 exons and is located on chromosome band 19q13 (66, 67). By analyses of numbers of ST2A3 genes, three allele variants with amino acid changes were identified (13). ST2A3*2 allele contains a T → C mutation at ST2A3 cDNA nucleotide 170, located within exon 2, resulting in a Met 57 → Thr change in the amino acid sequence. Another allele (ST2A3*3) contained an A → T mutation at nucleotide 557 within exon 4 resulting in a Glu 186 → Val change, as shown in Table 2. Recombinant ST2A3*2 (Met57Thr) and recombinant ST2A3*3 (Glu186Val) were shown to have decreased the thermal stability and activity for dehydroepiandrosterone as compared to the wild type (ST2A3*1). The allele frequencies for ST2A3*2 and ST2A3*3 are reported to be 0.024 and 0.038, respectively (13).

SULT2B

SULT2B1 was originally identified through the EST database from a human placenta cDNA library (16). The rapid amplification of cDNA end studies provided evidence that two ST2B1s (ST2B1a and ST2B1b) are transcribed from the same gene. ST2B1a and ST2B1b have different N-terminal amino acid sequences, which are transcribed from different exons as shown in Figure 2. ST2B1a is derived only from exon 2, whereas ST2B1b is from exon 1 and a part of exon 2. ST2B1a and ST2B1b thus consist of 350 and 365 amino acids, respectively, whose C-terminal sequences (342 amino acids) transcribed from a part of exon 2 to exon 6 are identical. Both forms are reported to catalyze sulfation of dehydroepiandrosterone, but not of other typical substrates for other SULTs (16). ST2B1 is expressed in human placenta, prostate, and trachea, and also slightly in the small intestine and lung. ST2B1 is on the long arm of chromosome 19 within band 19q13.3, which is the location similar to that of ST2A3 with an approximately 500-kb distance (16). Data on the genetic polymorphism are not yet available.

SULT5A

This SULT gene was identified by the Human Chromosome 22 Project Group. Information on the expression and enzymatic properties is not yet available. A part of the sequence is, however, observed in the EST database from human infant brain. The similar SULT sequence (St5a2) is also identified in the mouse brain cDNA library, although characterization of the St5a2 property has not been performed. It is worthwhile to note that amino acid sequences of both forms share 98% identity. These high sequence identities may suggest an important role of SULT5A in brain function.

SUMMARY AND FUTURE DIRECTIONS

A large number of cytosolic sulfotransferases has been identified from mammals and classified into five families based on their amino acid sequences. Recent studies on genetic polymorphism of SULT provide considerable amounts of information on allelic variants. These types of genetic information will likely increase in the near future.

The nomenclature system for SULTs is not yet universal, and confusion has already appeared. For this reason, we have proposed a comprehensive SULT nomenclature system. Cytosolic sulfotransferase (CST) other than those in mammals can be included based on structural similarity. Information on membrane-bound types of sulfotransferase (MST) is also increasing, but a relationship

between CST and MST remains unclear. Family numbers of SULT for vertebrates start from 1 for vertebrates, as shown above. Nonvertebrate forms may be started from 50, plant forms from 100, and bacteria forms from 200. We hope that this nomenclature system will be discussed and adapted and will be useful in the sulfotransferase research field.

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