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Pharmacogenetics of human sulfotransferases and impact of amino acid exchange on Phase II drug metabolism

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Sulfotransferases (SULTs) are Phase II drug-metabolizing enzymes (DMEs) catalyzing the sulfation of a variety of endogenous compounds, natural products, and drugs. Various drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDS) can inhibit SULTs, affecting drug–drug interactions. Several polymorphisms have been identified for SULTs that might be crucial for interindividual variability in drug response and toxicity or for increased disease risk. Here, we review current knowledge on non-synonymous single nucleotide polymorphisms (nsSNPs) of human SULTs, focusing on the coded SULT allozymes and molecular mechanisms explaining their variable activity, which is essential for personalized medicine. We discuss the structural and dynamic bases of key amino acid (AA) variants implicated in the impacts on drug metabolism in the case of SULT1A1, as revealed by molecular modeling approaches.

Keywords: Sulfotransferase; Pharmacogenomics; In silico modeling; Drug metabolism; Drug–drug interactions

Introduction

DMEs are responsible for the metabolism of endogenous molecules, such as steroid hormones and neurotransmitters, and a variety of xenobiotics and drugs. Phase I DMEs are mainly involved in oxidoreduction reactions, whereas Phase II DME catalyze conjugation reactions. Genetic variations resulting from nsSNPs contribute to the interindividual variability in the activity of Phase I DMEs, the main one being cytochrome P450 (CYP)[1–5] and of Phase II DMEs, including cytosolic sulfotransferases (SULTs)[6] and uri-



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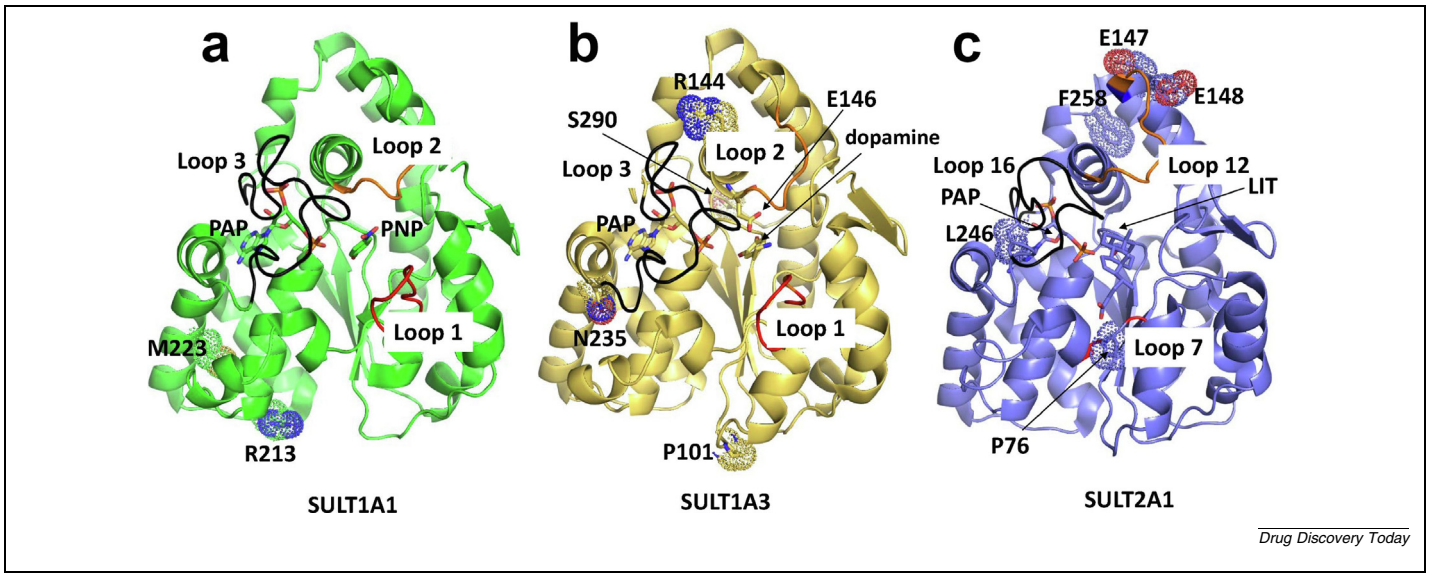


FIGURE 1

Crystal structures of sulfotransferases (SULTs). **(a)** Structure of SULT1A1 [Protein Data Bank (PDB) ID: 4GRA][111] The superposed reference substrate *p*-nitrophenol (PNP) is shown as sticks. **(b)** Structure of SULT1A3 (PDB ID: 2A3R).[118] The co-crystallized reference substrate dopamine is shown as sticks. **(c)** Structure of SULT2A1 (PDB ID 3F3Y). The co-crystallized substrate lithocholic acid (LIT) is shown as sticks. The loops surrounding the binding site are labeled. Amino acid (AA) substitutions known to decrease the sulfation by >30% are shown as dots. The cofactor PAP is shown as sticks for the three SULT structures.

dine 5′-diphospho-glucuronosyltransferases (UGT).[7] SULTs are a supergene family catalyzing the transfer of the sulfonate group from the co-factor 3′-phosphoadenosine 5′-phosphosulfate (PAPS) to a hydroxyl or amino group of substrates.[8,9] Human cytosolic SULTs include 12 enzymes classified into four families, SULT1, SULT2, SULT4 and SULT6, which are found in many tissues.[10] SULT family members share the same fold (Fig. 1) and at least 45% AA sequence identity and members of each subfamily share more than 60% AA sequence identity. SULTs metabolize a broad variety of substrates, including endogenous compounds, such as catecholamines, steroids, natural compounds,[11,12] and drugs.[8] NSAIDs inhibit cytosolic sulfotransferases with therapeutically relevant affinities, and molecular mechanisms of drug interactions for different SULT isoforms have been shown,[13–18] as schematized by Marto *et al.*[19] For each SULT isoform, many identified polymorphisms[20,21] might be crucial for interindividual variability in drug response and toxicity or for increasing some disease risks.[6,22]

Although noncoding SNPs (ncSNPs) affecting expression and gene copy number variation (CNV) might also contribute to variability, we review here current knowledge on nsSNPs of human SULTs, focusing on the purified SULT allozymes. Some nsSNPs resulting in AA substitutions (Table 1) have a significant impact on protein structure and function. Nevertheless, the molecular mechanisms explaining their variable activity need to be understood further to make more accurate predictions regarding potential new ligands and personalized medicine. We also discuss the structural and dynamic bases of key AA variants of SULT1A1 affecting the drug metabolism.

Major members and polymorphisms of *SULT1*

The human SULT1A subfamily includes four *SULT* genes (resulting from ancestral *SULT1A1* gene duplication), encoding three SULT isoforms: SULT1A1 and SULT1A2, and SULT1A3/SULT1A4. The open reading frames (ORFs) of *SULT1A3* and *SULT1A4* differ by only a single nucleotide change that does not alter the encoded AA, making difficult to ascribe individual polymorphism to *SULT1A3* versus *SULT1A4*. Yet, because of differences in gene localization and promoter identities, SULT1A1–4 do not have identical tissular expression.

SULT1A1

SULT1A1, also known as the thermostable phenol sulfotransferase, the most abundant SULT in human liver, is also expressed in lung, platelets, kidney, and gastrointestinal tissues.[23] SULT1A1 exhibits the broadest substrate range, with specificity for phenolic compounds, including aromatic amines, hydroxylamines, hydroxamic acids, alcoholic steroids, and various promutagen compounds (benzylalcohols, secondary nitroalkanes, and polycyclic aromatic hydrocarbons, which might form DNA adducts once sulfated).[8,14,22,24,25] SULT1A1 responsible for the sulfation of widely used drugs, including acetaminophen[26] or NSAIDs, such as desmethylnaproxen (*O*-DMN, a major metabolite of naproxen).[27,28] The reference *in vitro* substrate for SULT1A1 is 4-nitrophenol (*p*-nitrophenol, PNP), which has a higher affinity for SULT1A1/2 than for other human SULT isoforms.[29,30]

The gene encoding SULT1A1 is on the short arm of chromosome 16.[31] The most frequent SULT1A1 polymorphisms identified (Table 1) are SULT1A1*1 (the wild type, WT), SULT1A1*2 containing the AA substitution R213H, and SULT1A1*3 containing the M223V substitution. There are significant differences in the sulfation activities of SULT1A1*1, SULT1A1*2, and SULT1A1*3, with SULT1A1*2 activity being drastically reduced because of lower catalytic activity and thermostability.[22,32–34] In general, the trend order in V_{max} estimates is *1 > *3 > *2, but might differ for a few substrates, with K_m also slightly affected.[35] The sulfation activity of SULT1A1*2 is drastically decreased

TABLE 1

Frequencies of the major sulfotransferases *SULT1* and *SULT2* alleles in different populations.[a]

Allele	Genome identifier	Amino acid replacement	Allele frequency in Caucasians (%)	Allele frequency in Asians (%)	Allele frequency in Africans, African-Americans (%)	Refs
SULT1A1*1	–	–	65.6	91.4	47.7	33
SULT1A1*2	rs1042028	R213H	33.2; 31.2	12.0	29.4; 31.1	33,21
SULT1A1*3	rs1801030	M223V	1.2	0.6; 0.1	22.9	21,33
SULT1A1*4	rs72547527	R37Q	0.3	NA	NA	32
SULT1A2*1	–	–	50.8; 50.7	92.4	63.7	49,33
SULT1A2*2	rs1136703. rs1059491	I7T, N235T	28.7; 38.9; 31.6	7.6; 10.3	24.9	49,33,21
SULT1A2*3	rs10797300	P19L	18.0; 10.4; 11.5	ND	11.4	49,33,21
SULT1A3*2	rs1328799050	K234N	ND	NA	2.5; 4.2	54,62
SULT1A3*3	rs751527244	P101L	ND	NA	2.5	54
SULT1A3*4	rs751527244	P101H	ND	NA	0.4	54
SULT1A3*5	rs1293732453	R144C	ND	NA	2.5	54
$SULT1B1^{WT}$	–	–	100	100	91.3	70
$SULT1B1^{L145V}$	rs11569736	L145V	ND	ND	8.7	70
SULT1C2*2	rs17036104	S255A	6.7	NA	NA	73
SULT1C2*3	rs72549391	D60A	1.1	NA	NA	73
SULT1C2*4	rs17036058	R73Q	1.1	NA	NA	73
SULT1C2*5	rs72549392	S111F	0.6	NA	NA	73
SULT1E1*2	rs11569705	D22Y	15.0	NA	0.8	83,51
SULT1E1*3	rs34547148	A32V	0.8	NA	ND	83
SULT1E1*4	rs11569712	P253H	0.8	NA	ND	83
SULT2A1*2	rs972423172	M57T	2.7	NA	NA	119
SULT2A1*7	rs11569681	A63P	NA	NA	4.4–7.3	83
SULT2A1*8	rs11569680	K227D/E	NA	NA	0.8	41
SULT2A1*9	rs11569679	A261T	NA	NA	10.1–14.1	41
SULT2B1b	rs16982158	D191N	NA	NA	0.8	120
SULT2B1b	rs16982169	R230H	NA	NA	0.8	120
SULT2B1b	rs17842463	P345L	2.5	NA	NA	120

[a] *Abbreviations:* NA, information not available; ND, no allele detected.

against various substrates, such as estrogens, iodothyronines, or 1′-hydroxysafrole (Table 2). At relatively low PAPS concentrations, typically <20 mM,[36] SULT1A1*3 exhibited almost no activity toward estradiol (E2) but some activity toward 2-hydroxyestradiol (2OHE2),[35] suggesting that the bulky 2OHE2 stabilizes this alloform. Significant sulfation differences were also observed between SULT1A1*1, SULT1A1*2, and SULT1A1*3 toward various flavonoids (Table 2). SULT1A1*1 and SULT1A1*2 were also found to catalyze the sulfation of lignans with antitumor properties,[11] or verproside and its metabolites,[37] with slight differences between the activities of the two allozymes. Interestingly, some flavonoids with moderate SULT-mediated sulfonation have been found to potently inhibit SULT enzymatic activities in a mixed noncompetitive manner.[38] The M223V variant (SULT1A1*3), which is well represented in African-Americans, is not always taken into account in drug development; consequently, in some studies, the isoforms referred as SULTA1*1 versus SULT1A1*2 (R213H) can also include variation at position 223. In a recent study, Rasool and collaborators[39] analyzed the sulfation activity of nine SULT1A1 recombinant allozymes resulting from different AA exchange on the SULT1A1*3 backbone. AA substitutions F247L and M77I resulted in moderately higher sulfation activity against the prototypic ligand PNP, acetaminophen, *O*-DMN, and tapentadol, whereas R37Q, P47S, H149Y, Y169D, T227P, or V243D exchanges resulted in lower sulfation activities, with SULT1A1*3/T227P showing the most significant activity reduction.[39]

Interestingly, the tamoxifen metabolite, 4-hydroxytamoxifen (OHT), can be sulfated by SULT1A1, SULT2A1, and SULT1E1.[40] As for many ligands, SULT1A1*2 (R213H) exhibits a lower sulfation activity toward OHT.[35,41] This has fostered studies on *SULT1A1* polymorphism association with increased risk of some cancers, such as breast cancer, particularly in Asian populations,[42] tongue cancer in women,[43] or gastric cancer.[44] An increased risk of oral squamous cell carcinoma has been also reported in the Taiwanese population with H149Y haplotypes.[45] By contrast, SULT1A enzymes can bioactivate tobacco or dietary pro-carcinogens, such as 2-amino-α-carboline,[46] which might contribute to complex environment–SULT genotype interactions that are difficult to appraise from small studies.[47]

SULT1A2

Resulting from gene duplication during evolution, the sequence similarity between SULT1A1 and SULT1A2 is 96%, with only eleven distinct AA residues.[10,22] SULT1A2 mRNA has been detected in human liver, but, unlike SULT1A1, not in extra-hepatic tissues[48]; SULT1A2 might also sulfonate a variety of small planar phenols, iodothyronines, and estrogens, as seen with SULT1A1, but with lower catalytic activity.[8] As with SULT1A1, recombinant SULT1A2 sulfonates polycyclic aromatic hydrocarbons (PAHs),

TABLE 2

Relative sulfation activity of SULT1A1*2 and SULT1A1*3 toward endogenous and xenobiotic compounds compared with the sulfation activity of WT[a]

Compound	Apparent K_m for SULT1A1*1 (μM)	Comparative activity for SULT1A1*2	Comparative activity for SULT1A1*3	Refs
PNP	3–4	- -	–	35,61
2-Naphtol (biomarker of PAH exposure)	0.1	- -		45,108
Apigenin	1.7	- -	–	121
Epicatechin	242	- -	– (+)	121
Resveratrol	2.3	- -	– (+)	121
Chrysin	2.5	- -	– (+)	35
Quercetin	33.5	–	– (+)	35
Genistein	6.5	- -	– (=)	35
Silydianin and taxifolin (flavonolignans)		=		11
Aminoflavone (anticancer prodrug)	(Biological assay)	–	+	122
E2	31	n.e.	n.e.	82
	5			35
	1			108
2OHE2	2.5		–	82
	3.4	- -	(+)	35
2-methoxyestradiol (2MeE2)	11	- -	– (=)	35
OHT (antiestrogen/anticancer agent)	14	- -	–	35
	0.8			40
	0.6 and 13			36
Prohormone T4Triiodothyronine (active T3)	100	–		34
	84			
3,5,3′-Triiodothyronine (rT3)	36			
3,3′-Iodothyronine (T2)	0.5			
ABT-751 (anticancer agent)	88	- -	- -	123
1′-Hydroxysafrole (carcinogenic metabolite of safrole)		- -		45
Catalposide (anti-inflammatory, antioxidant)	162	– (+)		124
Verproside (anti-inflammatory, antioxidant)	0.7	+		37
Picroside II (metabolite of verproside)	9	=		37
Isovanilloylcatalpol (metabolite of verproside)	9	+		37
Acetaminophen (paracetamol)	394 (R213,V223)	– (H213,V223)		39

[a] Comparative *in vitro* activity was compiled from reported V_{max} values (and trends from V_{max}/K_m values in brackets when it differed from V_{max} trend estimates): - -, strongly decreased; –, decreased; =, similar; +, increased; n.e., not estimated/activity too low; empty cell, not tested. N.B.: Apparent K_m values might be higher in some studies because of the lower PAPS cofactor concentration used in the assay.[36]

aromatic hydroxylamines, and hydroxamic acids more efficiently compared with other SULT isoforms; once sulfated, such compounds can form DNA adducts promoting mutagenicity.[25]

Six main SULT1A2 allozymes have been identified (Table 1): SULT1A2*1 (WT), SULT1A2*2 (I7T and N235T), SULT1A2*3 (P19L), and rare variants SULT1A2*4 (I7T, R184C, and N235T), SULT1A2*5 (I7T), and SULT1A2*6 (N235T).[21,25,33,49] SULT1A2*2 exhibits enhanced thermostability and SULT1A2*3 shows decreased thermostability compared with SULT1A2*1[25]; The variants 1A2*1, 1A2*3, and 1A2*5 showed higher sulfation activity for PNP compared with the variants 1A2*2 and 1A2*6,[25] and, accordingly, SULT1A2 variants exhibit distinct mutagenic activities for 1-hydroxymethylpyrene, *N*-hydroxy-2acetylaminofluorene, and 2-hydroxylamino-5-phenylpyridine, increasing in the order 1A2*1 > 1A2*5 > 1A2*3 > 1A2*6 > 1A2*2.[25] However, due to a splicing defect, SULT1A2 RNA is poorly translated in humans, leading to very low levels of proteins in normal tissues.[49,50] Nevertheless, the influence of *SULT1A2* polymorphism might have biological implications if re-expression occurs in deregulated cells, such as cancer cells. Indeed, *SULT1A2**2 and *SULT1A2**3 variants have been associated with a higher blood concentration of tamoxifen metabolites (OHT and endoxifen) in patients with breast cancer.[51] In parallel, *in vitro* and *ex vivo* models revealed that a high level of expression of SULT1A1 or SULT1A2 in breast cancer cells might confer resistance to tamoxifen therapy.[52] Whether individuals harboring certain ncSNPs affecting SULT1A1/2 expression (such as in the 3′-untranslated region, UTR)[53] with specific nsSNP variants are more sensitive to chemotherapy remains to be explored on a large scale.

SULT1A3

SULT1A3 is encoded by two genes, *SULT1A3* and *SULT1A4,* located on chromosome 16, and likely derived by gene replication during evolution.[54] SULT1A3 is expressed in the highest concentration in the intestine, but is also found in brain, lung, and platelets, and in a very low concentration in liver.[49,55] It shares ~93% AA identity with SULT1A1 and preferably sulfonates monoamines, including indolamines (serotonin and melatonin) and biogenic catecholamines (dopamine, epinephrine and norepinephrine).[29] It also sulfonates structurally related compounds, iodothyronines[56] and dietary xenobiotics (catechin, hesperetin, chrysin, epigenin,[38] and curcuminoids[57]), acetami-

TABLE 3

Relative SULT1A3 activities toward bioamines and drugs with main allozymes and selected amino acid substitutions.[a]

Substrate	K_m for WT (μM)	Amino acid substitution: activity compared with WT												Refs
		(*2) K234N	(*3) P101L	(*4) P101H	(*5) R144C	T7P	S8P	R9C	P10L	V15M	V18F	N235T	S290T	
Dopamine (reference substrate)	6.5	–	–, =	–	=	=	=	=	=	=	=	–	=	54,63
Epinephrine	9.2	=	=	=	=	=	=	=	=	=	=	- -	=	63
Norepinephrine	10.7	–	=	=	–	–	–	- -	–	–	–	- -	–	63
Serotonin	71.4	–	- -	=	- -	=	=	- -	–	–	–	- -	- -	63
Tapentadol	150	- -	=	+	+	=	- -	- -	- -	- -	- -	- -	=	64
Morphine	4600	- -	=	+	=	=	–	- -	–	=	–	- -	–	64
O-desmethyl tramadol	460	–	=	+	+	- -	- -	- -	=	–	- -	- -	=	64
Acetaminophen	630	– (=)	–	=	–	=	–	- -	–	=	–	- -	–	64
Ritodrine	122	–	–	- -	–									60

[a] Comparative *in vitro* activity compiled from reported specific activities (V_{max} or V_{max}/K_m) compared with WT: - -, strongly decreased; –, decreased; =, similar; +, increased; empty cell, not reported.

nophen, NSAIDs, and opioid or adrenergic drugs.[58–60] The residue E146 (Fig. 1b) has an important role in SULT1A3 selectivity, because its change to A146 turns SULT1A3 into a SULT1A1-like enzyme.[61] Moreover, the presence of both carboxylic groups E146 and D86 is key for the recognition of the amino group of the dopamine substrate.[15]

Several nsSNPs leading to AA alterations have been identified for *SULT1A3* and *SULT1A4* (Table 1). Table 3 illustrates the sulfation activity of the most studied AA variants against monoamines and drugs compared with that of WT allozymes. The SULT1A3*2 allozyme was estimated to be less resistant to proteasome-mediated degradation compared with SULT1A3*1,[62] possibly accounting for its apparent reduced sulfating activity.[63] The N235T substitution (Fig. 1b) showed the lowest activity against all tested substrates compared with other allozymes,[60,63,64] whereas increased catalytic activities of SULT1A3*4 or *5 allozymes compared with WT were reported against tapentadol, morphine, and *O*-desmethyl-tramadol (Table 3).

Interestingly, SULT1A3 might prevent the occurrence of adverse reactions by protecting neuronal cells from bioamine toxicity. Similarly, serotonin sulfation deficiency has been associated with hyperserotonemia in individuals with autism spectrum disorder.[65] Moreover, ethnic-specific inherited differences in catecholamine sulfation[62] have been associated with differential disease risks regarding cognitive disorders[6] and dopamine-dependent neurodegeneration,[66] possibly related to differential *SULT1A3* genetics, which still remain to be addressed.

SULT1B1

SULT1B1 (initially named ST1B2[67]) is the single member of the human SULT1B subfamily and might be involved in the physiological regulation of thyroid hormones.[6] The highest protein concentrations have been found in the mucosa of the gastrointestinal tract, the protein being also detected at lower concentrations in liver, lung, lymphoid tissues, and leukocytes.[55,68] The main substrates of SULT1B1 include iodothyronines, small phenolic compounds,[67] some flavonoids,[69] or lignans.[11] SULT1B1 displays no affinity for steroid hormones[14] but can sulfate drugs, such as raloxifene[40] or *O*-DMN.[27] It is also effective at sulfonating planar multi-ringed chemicals, such as PAHs and benzylic alcohols, to reactive intermediates that can form DNA adducts.[48]

The only reported nsSNPs with functional outcome is the African-descent specific variant (rs11569736), with SULT1B1-L145V showing slower PAPS turnover rate and significant decreased sulfation of PNP (but not 1-hydroxypyrene or 1-naphthol) compared with WT.[70] The impacts of this variant on other ligand interactions and on disease risk remain to be evaluated.

SULT1C

The human SULT1C subfamily includes four isoforms: SULT1C2 (previously referred to as SULT1C1), SULT1C3a/SULT1C3d, and SULT1C4, encoded by *SULT1C2*, *SULT1C3* and *SULT1C4*, respectively.[71] Relatively few endogenous compounds, thyroid hormones, and phenolic drugs can be sulfated by SULT1C enzymes.[14] Highly expressed in fetal tissues, SULT1C enzymes are likely to have an important role in the metabolism of xenobiotics and thyroid hormones during development.[14,72]

SULT1C2 is expressed in adult stomach, kidney, and thyroid gland.[71] It catalyzes the sulfation of PNP and iodothyronines.[6,73] Four nsSNPs for *SULT1C2* with low frequencies have been reported[73] (Table 1). The corresponding allozymes *3 and *4 showed significantly reduced enzyme activity toward PNP compared with *2 or WT, whereas SULT1C2*5 did not exhibit detectable activity toward this substrate.[73] Strikingly, *SULT1C2* tumoral gene expression is induced by tobacco exposure and is associated with better patient outcome in lung adenocarcinoma, suggesting that SULT1C2 serves as a detoxifying enzyme in this case.[74] Whether the lower *SULT1C2* promoter methylation status and corresponding higher *SULT1C2* expression in the normal lung in Asians compared with Caucasians[74] explain the known disparities in clinical presentation of this cancer remains to be explored. Thus, further studies taking into account SULT1C2 activity and better knowledge of nsSNP are needed.

Given the presence of different splicing sites,[75] *SULT1C3* can generate two SULT1C3 isoforms differing by 30 AA residues, with SULT1C3a mRNA expressed in intestinal tissues[76] and SULT1C3d mRNA expressed in placenta and skeletal muscle.[76] So far,

TABLE 4

Relative sulfation activities of SULT1E1 allozymes toward endogenous and xenobiotic compounds.[a]

Substrate	Km for WT (μM)	Activity compared with WT								Refs
		(*2) D22Y	(*3) A32V	(*4) P253H	A43D	A131P	R186L	P214T	D220V	
E2	0.03; 2.1	- - (- -)	– (–)	1 (–)	= (–)	= (–)	– (–)	– (–)	– (–)	83, 86
4OH-tamoxifen	29.4				- - (- -)	= (- -)	– (-)	– (-)	- - (- -)	86
Diethylstilbestrol	2.3				– (+)	– (–)	+ (–)	- - (- -)	– (–)	86

[a] Comparative *in vitro* activity compiled from reported specific activity V_{max} (V_{max}/K_m in brackets): - -, strongly decreased; –, decreased; =, similar; +, increased; empty cell, not reported.

SULT1C3d has not been detected in kidney, liver, platelets, testis, or prostate.[77] SULT1C3a displayed weak activities toward hydroxyl-chlorinated biphenyls,[75] whereas SULT1C3d exhibited broader substrate specificity toward bile acids, thyroid hormones, and hydroxyl-chlorinated biphenyls,[75] some small phenols and α-zearalenol,[14] benzylic alcohols derived from PAHs, and 1′-hydroxysafrole, a liver carcinogen.[77] Patients with hypertension can have a decreased response to candesartan administration linked to *SULT1C3* polymorphism.[78]

SULT1C4, initially reported as hydroxyarylamine (or acetylaminofluorene) sulfotransferase, is expressed at the mRNA level in fetal lung or kidney at high levels and in fetal heart and adult kidney, ovary, and neural tissues at low levels.[71,72] Recombinant SULT1C4 exhibits the broadest substrate specificity toward PNP, xenobiotic compounds including dietary polyphenols, and some drugs, such as doxorubicin and epirubicin.[14,57,79] The differential doxorubicin-sulfating activity of some recombinant SULT1C4 allozymes suggests a potential impact on drug metabolism among humans carrying corresponding genotypes.[80] However, this might depend on actual SULT1C4 protein expression, because the predominant splice variant lacking exons 3 and 4 produces relatively less stable protein.[81]

SULT1E1

SULT1E1 is expressed in many human tissues, including liver, jejunum, mammary epithelium cells, and reproductive tissues. Its high-affinity substrates are endogenous estrogens and catecholestrogens.[82,83] Indeed, SULT1E1 is not only crucial for regulating low estrogen concentrations in target tissues (sulfated estrogens being inactive on estrogen receptors), but might be involved in the regulation of estrogen-dependent carcinogenesis or in the mechanisms of endocrine disruption.[84] SULT1E1 can also sulfate other steroids and their analogs, including dehydroepiandrosterone, pregnenolone, or diethylstilbestrol (DES).[85,86] Other substrates are flavonoids, fulvestrant (a drug used for breast cancer treatment), the active metabolites of toremifene and tamoxifen, troglitazone (an oral antidiabetic), or tibolone.[9,40,87]

Several frequent allelic variants of SULT1E1 (Table 1) and rare variants (A43D, A131P, R186L, P214T, D220V) have been identified.[83,86] Overall, these allozymes exhibit diminished sulfation activity compared with the WT toward E2, 4OH-tamoxifen, and DES (Table 4).

Major members and polymorphisms of SULT2

The three members of the SULT2 family show overlapping substrate specificities toward a range of hydroxysteroids and have been shown to mediate the sulfation of the endogenous androgen dehydroepiandrosterone (DHEA), cholesterol, oxysterols, or pregnenolone. In addition to serving as steroid hormone precursors, DHEA, pregnenolone, and their sulfated metabolites produced in the nervous system are considered as neurosteroids that act as important neuromodulators.[88] SULT2A1 (the prototypic DHEA sulfotransferase) is highly expressed in the liver, intestine, and adrenal corte,x and catalyzes the sulfate conjugation of endogenous androgens, bile acids, oxysterols, and several drugs (budesonide, tolvaptan, raloxifene, 4-hydroxytamoxifen, tibolone, and buprenorphine).[40,89–91]

The members of SULT2B1 (hydroxysteroid sulfotransferases), SULT2B1a and SULT2B1b, are encoded by the same gene but differ in the first exon used.[13,92] SULT2B1b is highly expressed in reproductive tissues, small intestine, colon, lung, platelet, brain, and skin, whereas no expression of SULT2B1a protein has been detected in human tissues.[92] SULT2B1b sulfonates DHEA, pregnenolone, cholesterol, and oxysterols,[93,94] whereas SULT2B1a sulfonates DHEA and pregnenolone but not cholesterol.[93,95] Interestingly, SULT2B1 could influence inflammatory responses or tumor immune evasion by regulating cholesterol or oxysterol availability.[96,97]

The frequencies of *SULT2* alleles found in different populations are shown in Table 1. SULT2A1 and SULT2B1b polymorphisms could drive important differences in the sulfation of DHEA or pregnenolone.[98,99] The observed sulfation activities of SULT2 allozymes are shown in Table 5. Whereas SULT2A1*2, *4, *5, *7, and *9 showed similar sulfation activity, several AA substitutions lead to decreased catalytic activities compared with WT. AA substitutions strongly decreasing the sulfation activity of SULT2A1 (P76, E147, E148, L246, and F258) are indicated in Fig. 1c. The residues E147, E148 (in loop 12), and L246 (in loop 16) are far from the substrate binding site. However, the dynamics of the loops 12 and 16 are instrumental for substrate recognition.[18] Loop 7 carrying P76 is close to the substrate; thus, its replacement is expected to alter the binding. The residue F258L forms a hydrophobic sandwich with W254 and F150; thus, its replacements would destabilize this area. F258 is also a part of the zipper motif KTVE signaling the dimer formation for several SULTs.[100] Interestingly, *SULT2A1* polymorphism rs2910397 is associated with a decreased DHEA sulfate (DHEAS)/DHEA ratio,[101] whereas rs182420 and rs2547238 are linked to prostate cancer risk.[102] For *SULT2B1*, mutations leading to R274Q,[103] E78K, and R100W[104] variants are linked to autosomal recessive congenital ichthyosis.

TABLE 5

Relative comparative sulfation activity of SULT2 allozymes toward endogenous steroids and tibolone steroid drugs.[a]

Substrate	K_m for WT (μM)	Refs	SULT2A1 activity compared with WT															
			(*2) M57T	(*3) T90S	(*4) L159V	(*5) E186V	(*6) M57T/ E186V	(*7) A63P	(*8) K227E	(*9) A261T	(*10) A63P/ A261T	K44E	P76T	E147K	E148K	L246P	F258L	Q262E
Tibolone	13	91	= (+)	– (=)	+	= (+)	–	=	–	=	–							
DHEA	10	91	=	–	+	=	–	=	–	–								
		98										n.e.	- -	–	- -	- -	- -	–
Pregnenolone		98										n.e.	- -	–	- -	- -	- -	–
			SULT2B1b activity compared with WT															
			P69A	**G72V**	**T73M**	**R147H**	**D191N**	**R230H**	**S244T**	**R274Q**	**G276V**	**P345L**						
DHEA	36	99	- -	n.e.	- -	n.e.	–	–	–	–	n.e.	–						
Pregnenolone	8	99	- -	n.e.	- -	n.e.	–	–	–	- -	n.e.	–						
Cholesterol	21.9	125	- -	n.e.	- -	n.e.	–	–	–	- -	n.e.	–						

[a] Comparative *in vitro* activity was compiled from reported specific activities V_{max} (and V_{max}/K_m in brackets): - -, strongly decreased; -, decreased; =, similar; +, increased; n.e., no detectable activity; empty cell, not reported.

Other human SULT isoforms

SULT4A1 and SULT6B1 contain only one member per respective family.

SULT4A1, expressed in the brain, is involved in neuronal signaling or development.[105] So far, it is an atypical SULT with undetectable binding toward PAP/PAPS cofactor and undetectable activity toward biological and xenobiotic SULT ligands.[14,82]

SULT6B1 has been found in human kidney and testis, and the human isoform (with seven allozymes) is proposed to metabolize the sulfation of thyroxine (https://www.uniprot.org/uniprot/Q6IMI4). SULT6 from other species has been shown to sulfate several phenols and steroids[6]; however, such activities have not yet been reported in humans.

Finally, besides these nsSNP, ncSNPs affecting expression and gene CNV might also contribute to variability in drug or endogenous hormone/neurotransmitter metabolism.[106] CNV is increasingly appraised with disease risk, such as for Alzheimer's or early-onset Parkinson diseases.[66] As discussed above, some SNPs and CNVs are over-represented in ethnic populations,[106] both contributing to drug metabolism variation. Consequently, the combinatory influence of specific SNPs and CNVs challenges the analysis of drug pharmacokinetics and potential disease risk in personalized medicine approaches. With advances in whole-genome sequencing and increased understanding of promoter methylation and gene expression data,[107] such bioinformatics combinatory analysis will help to better predict the physiological relevance of the variation in SULT activity on drug properties.

In summary, the polymorphisms of SULTs can be crucial for the interindividual variability in drug response and toxicity or for increasing disease risk. The most abundant SULT in the human liver is SULT1A1,[23] which exhibits the largest substrate range and is able to modify diverse endogenous compounds, promutagen and procarcinogen xenobiotics, and drugs.[8,14,22,24,25] Significant differences have been observed in the sulfation activities of SULT1A1*1 and SULT1A1*2 (Table 2), with the latter having drastically reduced catalytic activity and thermostability.[22,32–34] Yet, SULT1A1*2 was the first to be extensively studied with the first 3D structure resolved by X-ray crystallography.[30] However, SULT1A1*1 is most frequent in the different populations, and SULT1A1*3 is also well represented in African-Americans (Table 1) but has been less studied. Strikingly, as can be seen from Table 2, SULT1A1*3 showed an increased affinity for some ligands in terms of V_{max}/K_m. Thus, to better understand and illustrate the molecular mechanisms affecting the catalytic activities of three major allozymes for SULT1A1, we performed *in silico* analyses which are presented in the following sections.

Case study: Role of AA substitutions in SULT1A1 variants on drug metabolism

The first crystal structure of SULT1A1 was reported for SULT1A1*2 [Protein Data Bank (PDB) ID: 1LS6].[30] Later, the structures of SULT1A1*1 (PDB ID: GRA) and SULT1A1*3 (PDB ID: 4Z28) were also resolved. Their comparison allows the analysis of structural bases involved in the altered metabolism of SULT1A1*2 and SULT1A1*3. The flexibility of SULT is a well-

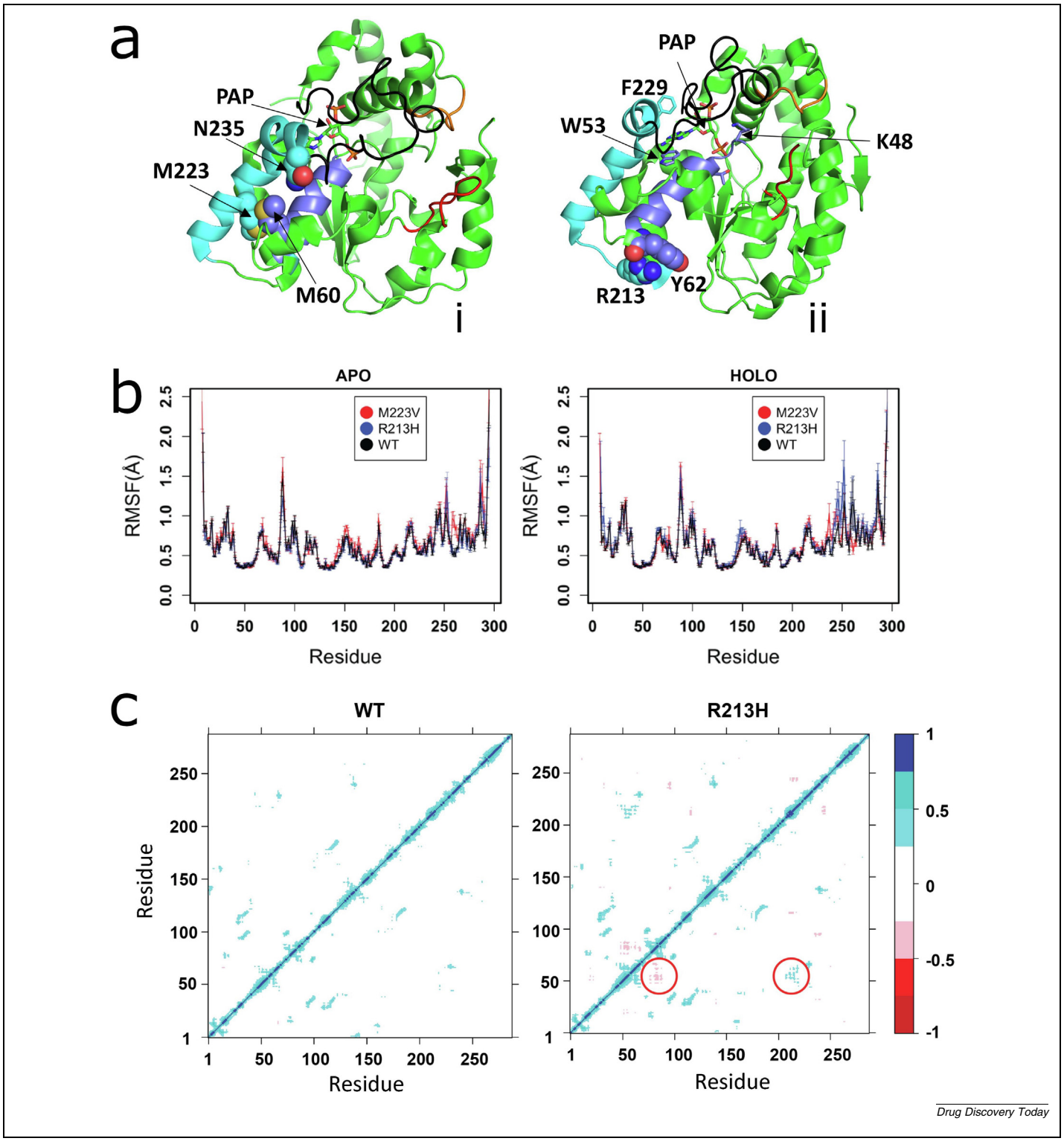


FIGURE 2

Structure and dynamics of sulfotransferase SULT1A1. **(a)** The replaced residues M223 (i) and R213 (ii) are presented as spheres. Key residues interacting with them are also shown as spheres. The α-helices carrying M223, R213, and their residues in contact are colored in cyan. **(b)** Root mean square fluctuations (RMSFs) from the simulations of the APO and HOLO SULT1A1 structures of SULT1A1*1, SULT1A1*2, and SULT1A1*3. For each structure, the RMSFs of each residue are averaged over three independent molecular dynamics (MD) runs of 40 ns. The error bar represents the standard error of the mean. **(c)** Protein residue cross-correlation analysis for SULT1A1*1 (wild type; WT) and SULT1A1*2 (R213H). Cross-correlation map is derived from the average pairwise correlation coefficients between protein residues obtained from the three independent MD runs of 40 ns. The positive values indicate positively correlated motions between two residues (e.g., the two residues move in the same direction) whereas negative values represent the anticorrelated motions. The strongest correlated and anticorrelated motions in R213H variant are encircled.

known phenomenon implicated in the recognition of highly diverse substrates.[44,108] In SULT1A1, three major loops, loop 1 (L1, called lip: residues 83–91), loop 2 (L2: residues 141–158) and loop 3 L3 (so-called 'cap': residue 235–255), surrounding the cofactor and substrate binding sites (Fig. 1) have important roles in substrate recognition.[17,109] Here, we analyzed the protein dynamics of the three alloforms SULT1A1*1 (WT), *2 (R213H) and *3 (M223V). As mentioned above, AA substitutions in the SULT1A1 variants R213H and M223V have been linked to decreased thermostability and/or altered enzymatic activity toward various substrates. Here, we explored the structural and dynamics bases of the mutations R213H and M223V to further delineate molecular mechanisms affecting the substrate recognition and metabolism. The locations of residues R213 and M223 are shown in Figs. 1a and 2a.

We used molecular dynamics (MD) simulations for the major allozymes of SULT1A1, *1, *2, and *3 to obtain insights into conformational flexibility changes resulting from the two mutations. We note here the alloforms with a bound substrate as 'HOLO', and without bound substrate as 'APO', respectively. The simulations of all structures were performed here in the presence of the bound cofactor PAP. Previous MD simulations[12,14,15,17,110] showed that PAPS and PAP have similar stabilizing effects on SULT structures. To perform MD simulations, we used the crystal structures of the SULT1A1 co-crystallized with the cofactor PAP [PDB IDs: 4GRA,[111] 2D06,[112] and 1Z28[113] corresponding to SULT1A1*1 (WT) in APO state, *2 (R213H) with bound 17β-estradiol ('E2') in HOLO state and *3 (M223V) in APO state, respectively]. We then built the structural models of SULT1A1, *1, *2, and *3 in both the HOLO and APO states (i.e., in the presence or absence of bound E2, respectively). We performed a structural alignment of 2D06 (HOLO state) to the APO structures (4GRA and 1Z28) and placed E2 of the 2D06 structure to model the HOLO structures of SULT1A1*1 and *3. To model the APO states, we removed E2 and kept only the cofactor. MD simulations were performed with NAMD 2.11[114] with Charmm36 force field[115] and the TIP3P water model.[116] Proteins were solvated with 0.15 M NaCl in cubic water box with at least 10 Å from the protein to the edge of box. Langevin dynamics with periodic boundary conditions were applied in the simulation. First, the system underwent a 5000-step minimization with a fixed backbone and a subsequent 5000-step minimization without constraint. Then, all atoms of the protein were fixed for 100 ps equilibration of the water. A harmonic constraint of 1 kcal•mol^{-1}•Å^{-2} was applied to the protein alpha carbon atoms (CA), and the system was then gradually heated from 0 K to 310 K with 1000-step/K in the NVT simulation. The system was maintained at 310 K for 1 ns equilibration with 1 kcal•mol^{-1}•Å^{-2} constraints on CA atoms and another 2 ns equilibration without constraints in NVT system. Finally, the system was switched to an NPT simulation and all constraints were removed.

To investigate the effects of the R213H and M223V mutations, we performed three production runs of 40 ns starting at different initial velocities for each structure of APO and HOLO states. The overall analysis time per enzyme state was 120 ns. The root mean square deviation (RMSD) analysis for our simulations indicated that the systems were stable during the 40-ns production run and we did not observe significant differences in the RMSD values between the SULT1A1*1, *2, and *3 variants in either the APO or HOLO states. We compared the root mean square fluctuation (RMSF) values of all structures to reveal the effects of mutations on the protein dynamics (Fig. 2b).

In the APO state of M223V, increased flexibility is observed for the three loops compared to the WT. In HOLO state of M223V, our results revealed significantly increased flexibility of the Lip and the beginning of the cap L3 (around residue 235) compared with WT. The end of the cap (around residue 260, which is far from the substrate binding site) became more rigid. Interestingly, M223 is in hydrophobic contact with M60 belonging to the same α-helix in tight contact with the 5′-phosphate of PAP (or with the phosphosulfate of PAPS) (Fig. 2ai). This hydrophobic contact appears to be lost in the M223V variant. It was previously suggested that a large dynamic shift of L3 occurs upon PAPS binding to allow large ligands to enter into the active site, whereas this is not necessarily required for small compounds to dock.[108] Remarkably, decreased sulfation has been reported for several large ligands (epicatechin, chrysin, resveratrol, quercetin, 2OHE2, and E2) for SULT1A1*3 compared with WT according to the V_{max} values, whereas increased affinities can be expected according to the observed V_{max}/K_m values (Table 2).[82] The slightly increased flexibility of the L3 region in the case of SULT1A1*3 detected by our simulations (Fig. 2b) likely facilitates the entering of large ligands, accounting for their higher affinity, whereas it destabilizes PAPS binding, explaining the slightly decreased sulfation activity observed.

In the HOLO state of R213H, loop L2 (around residue 150) and cap L3 (around residue 250) became significantly more flexible than in WT (Fig. 2b). Therefore, we performed dynamic cross-correlation analysis of protein residues to compare WT and R213H, which showed additional differences between the WT and R213H variant (Fig. 2c). In the case of R213H, we observed increased anticorrelated motions around the lip. Correlated motions between residues 210 and 230 (in contact with the adenosine part of PAP and a part of the α-helix carrying residue 213) and 48 and 52 (in contact with the 5′-phosphate of PAP and a part of the α-helix carrying Y62) were obtained for R213H, which were not present in WT. In the R213H variant, the hydrogen bond (HB) between the side chain of R213 (belonging to the terminal of an α-helix linked to the cap) and the backbone carbonyl of Y62 is lost, which explains the increased flexibility of its cap. Furthermore, the correlated motions can be explained by the fluctuations of the cofactor in tight contacts with the two segments 210–230 and 48–52 (Fig. 2aii). Such correlated motions are not seen in WT, possibly because the HB present stabilizes the interactions between the helices of these two segments. Our results are consistent with a recent study of SULT1A1*2 (R213H),[117] showing that R213H mutation induced local conformational changes, especially in cap L3 (Fig. 2a) rather than impairing overall stability of the protein structure. The authors predicted that the binding energy of PNP increased from –120 kJ/mol for WT to –115 kJ/mol for the R213H variant in agreement with its experimental affinity to PNP, which is considerably decreased compared with WT (Table 2).

In conclusion, the variants R213H and M223V alter the protein dynamics, which is crucial for substrate recognition and

PAP/PAPS binding. The R213H allozyme changes considerably the dynamics of its three loops surrounding the substrate binding site, and a dramatic flexibility increase in the L3 cap involved in the PAPS interaction is observed. For the M223V variant, we obtained less-important changes, which correlated with the experimental data showing that, overall, for most of the SULT1A1 substrates, SULT1A1*3 has slightly decreased sulfation activity compared with WT but might accommodate larger compounds (Table 2).

Concluding remarks

SULTs are important enzymes participating in Phase II metabolism catalyzing the sulfation of a large variety of endogenous compounds, natural products, and drugs. NSAIDS and dietary polyphenolic compounds are able to inhibit SULTs, thus possibly interfering with the bioavailability of drugs or endogenous physiological compounds. SULTs display broad interindividual variability with ethnically dependent genetic variation, such as coding or noncoding SNPs and CNVs. Altered SULT activity in response to disease conditions and genetic variations could have clinical consequences, such as xenobiotic toxicity, drug response, or alteration of normal homeostasis. The influence of SULT genotype–disease risk association has begun to be investigated. However, *in vivo* studies of drug (or their metabolic intermediates) sulfonation in humans are still limited, likely because of the difficulties of implementing large cohort studies associated with full genetics analysis and the complex interplay between diet, drugs,and SULT polymorphism. Current understanding of *in vitro* studies of coded SULT allozymes sheds light on the molecular mechanisms that explain their intrinsic variable activity. As seen from the case study analysis of SULT1A1, molecular modeling approaches are particularly useful to better understand how a single AA variant can affect substrate or cofactor binding and the sulfation activity involved in drug toxicity or in endogenous metabolite homeostasis. Accumulation of numerous *in vitro* data and whole-genome sequencing in near future would be instrumental, in addition with progress of AI approaches for Phase II drug-metabolizing SULT enzymes, for the prediction of altered sulfation activity and drug response, which will be essential for developing personalized medicines.

Data availability

No data was used for the research described in the article.

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