

Copy number variation in sulfotransferase isoform 1A1 (*SULT1A1*) is significantly associated with enzymatic activity in Japanese subjects

Xinfeng Yu¹
Takahiro Kubota²
Ishwori Dhakal¹
Setsuo Hasegawa³
Suzanne Williams¹
Shogo Ozawa⁴
Susan Kadlubar¹

¹Division of Medical Genetics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; ²Chiba Institute of Science, Chiba, Japan; ³Sekino Clinical Pharmacology Clinic, Tokyo, Japan; ⁴Iwate Medical University, Iwate, Japan

Abstract: Sulfotransferase isoform 1A1 (*SULT1A1*) plays a key role in the metabolism of a variety of endo- and xenobiotics and its activity could influence response to drugs. Our previous studies have focused on the impact of genetic variants of *SULT1A1* on enzymatic activity in Caucasians and African-Americans. However, the contribution of genetic variants to *SULT1A1* activity in Asians has not been explored. In this study, we investigated the collective effects of both *SULT1A1* copy number variants (CNVs) and single nucleotide polymorphisms (SNPs) in the promoter region, coding region, and 3' untranslated region on *SULT1A1* activity in Japanese subjects. SNPs in the *SULT1A1* promoter and 3' untranslated region were not associated with *SULT1A1* activity ($P > 0.05$). *SULT1A1**1/2 (Arg213His) was marginally associated with *SULT1A1* activity ($P = 0.037$). However, *SULT1A1* CNVs were strongly associated with *SULT1A1* activity (trend test $P = 0.008$) and accounted for 10% of the observed variability in activity for Japanese subjects. In conclusion, *SULT1A1* CNVs play a pivotal role in determination of *SULT1A1* activity in Japanese subjects, highlighting the influence of ethnic differences in *SULT1A1* genetic variants on drug metabolism and therapeutic efficacy.

Keywords: CNV, genotype, phenotype, *SULT1A1*, single nucleotide polymorphisms

Introduction

Sulfotransferase isoform 1A1 (*SULT1A1*) belongs to a family of phase II detoxification enzymes that catalyze the transfer of the sulfonyl group from 3'-phosphoadenosine 5'-phosphosulfate to a variety of endogenous molecules (hormones, neurotransmitters, etc) and xenobiotics.¹ Sulfation generally enhances the solubility and subsequent excretion of substrates, but it can also catalyze the bio-activation of various carcinogens and mutagens.^{2,3} The growing field of pharmacogenomics seeks to predict both efficacy and toxicity of therapeutic agents, many of which are substrates for *SULT1A1*. *SULT1A1* metabolizes many drugs, including tamoxifen,⁴ fulvestrant,⁵ and toremefine,⁶ which are used for adjuvant hormonal therapy in breast cancer. Given the central role that *SULT1A1* plays in drug metabolism and carcinogenesis, elucidation of the genetic determinants of *SULT1A1* activity is essential in assessing the therapeutic efficacy of drugs and estimating cancer risk.

Abnormal expression and/or enzymatic function of *SULT1A1* resulting from naturally occurring genetic changes, such as single nucleotide polymorphisms (SNPs) and copy number variants (CNVs), may influence drug metabolism. A common SNP in the coding region of *SULT1A1* (638 G > A, *SULT1A1**1/*SULT1A1**2) is associated with decreased platelet enzymatic activity and thermostability.^{7,8} This SNP has been investigated in relation to risk of cancer in various organs and tissues in different ethnic

Correspondence: Susan Kadlubar
University of Arkansas for Medical Sciences, 4301 W Markham, #580, Little Rock, AR, USA 72205
Tel +1 501 526 7957
Fax +1 501 686 6639
Email sakadlubar@uams.edu

groups, with conflicting results in some instances.⁹ The 638 G > A SNP has been associated with risk of lung cancer,¹⁰ colorectal cancer,^{11,12} urothelial cancer,¹³ prostate cancer,¹⁴ and breast cancer^{15,16} in relation to smoking status and intake of meat that is cooked well done. *SULT1A1* 638 G > A has also been reported to influence overall survival in tamoxifen-treated women.^{17,18} Ning et al¹⁹ described four common (–624 G > C, –396 A > G, –341 C > G, and –294 T > C) and one rare SNPs (–358 A > C) in the proximal promoter region and found that allele frequencies varied between Caucasians, African-Americans, and Chinese subjects. These SNPs were associated with platelet *SULT1A1* enzymatic activity in Caucasians and African-Americans, but platelets for activity analyses were not available for the Chinese population. Thus, the association of the promoter SNPs with *SULT1A1* activity in individuals of Asian descent was not explored. We have recently reported that 902 A > G and 973 C > T in the 3′ untranslated region (3′-UTR) and 1307 G > A in the 3′ flanking region play an important role in determination of *SULT1A1* activity in Caucasians and African-Americans. These SNPs, in combination with *SULT1A1* CNVs, account for 21% of variability of activity observed in Caucasians.²⁰

In this study, DNA from 97 Japanese subjects was screened for *SULT1A1* 638 G > A, promoter SNPs, 3′-UTR, and CNVs. Platelets were also obtained and enzymatic activity determined, and genotype–phenotype relationships were examined. There was a significant ethnic difference in the influence of genetic variants on *SULT1A1* activity, with copy number variation exhibiting the strongest influence. Hence, pharmacogenomic studies of *SULT1A1* substrates should include *SULT1A1* CNVs, particularly in Japanese populations.

Materials, subjects, and methods

Materials

Histopaque®-1119 and -1077, 4-nitrophenyl sulfate, and 2-naphthol were obtained from Sigma-Aldrich (St Louis, MO, USA). The 3′-phosphoadenosine 5′-phosphosulfate was obtained from the University of Dayton Chemistry Department (Dayton, OH, USA). Sequencing and polymerase chain reaction (PCR) primers were purchased from Invitrogen (Grant Island, NY, USA). All other chemicals used were of reagent grade and obtained from Fisher Scientific (Houston, TX, USA).

Study subjects

Whole blood specimens (10 mL) were obtained from 101 healthy Japanese subjects recruited at the Chiba Institute

of Science. The specimens were drawn using Vacutainer™ tubes (Becton Dickinson, Franklin Lakes, NJ, USA and Fisher Scientific) containing ascorbate, citrate, and dextrose to prevent platelet aggregation. Of the 101 specimens obtained, 97 were evaluable for *SULT1A1* genotype–phenotype analysis. There were 55 female and 42 male subjects (age range 22–70 years old, mean 36.4 years). The Institutional Review Board at Chiba Institute of Science approved these study protocols (Ethics Committee approval No 22-8).

Preparation of platelet cytosols and sulfotransferase activity assay

Immediately after collection, the whole blood samples were layered on a discontinuous gradient of Histopaque-1077 and Histopaque-1119, using a modification of the manufacturer's protocol,^{8,21} then individual components were separated by differential centrifugation. After separation, platelets were suspended in buffer, membranes were disrupted by sonication, and the cell homogenate was subjected to ultracentrifugation at 100,000 g for 1 hour. Sulfotransferase activity was determined using a simple colorimetric procedure as described by Mulder et al²² with the modifications made by Frame et al.²¹ Activity was reported as nmol/min/mg protein.

DNA extraction and genotyping

DNA was extracted from lymphocytes isolated from the blood sample provided by the study participants using Qiagen extraction kits according to the manufacturer's instructions (Valencia, CA, USA). Genotyping for *SULT1A1**1/2, promoter SNPs, and 3′-UTR SNPs was performed as previously described.^{8,19}

Copy number variation assay

SULT1A1 copy number was determined by real-time PCR in an ABI PRISM Sequence Detection System 7900 Instrument (Applied Biosystems, Foster City, CA, USA) using TaqMan Gene Expression Absolute Quantification Assay (Applied Biosystems, Foster City, CA, USA). The method has been described by Yu et al.²⁰

Distal promoter SNP identification and genotyping

The human *SULT1A1* genomic sequence (GenBank® accession no U52852) was used to design three pairs of primers (P1, P2, and P3) to produce overlapping amplicons spanning from –165 to –2513 bp for distal promoter mutation screening. After mutation screening, two common SNPs, –1975 G > C and –1135 G > A, were identified and

a new pair of primers (P4) was designed for sequencing of –1975 G > C. The sequencing primer of P1 was used to identify –1135 G > A. Primer sequences are shown in Table 1. PCR was performed using JumpStart RED Taq-Reaction Mix (Sigma-Aldrich) 5 µL in a total volume of 10 µL containing 3 ng genomic DNA and 0.5 µM each of primers. PCR was amplified under the following thermal cycling conditions: after initial denaturation at 95°C for 4 minutes, the samples were subjected to 35 cycles of 94°C for 50 seconds, 64°C for 50 seconds, and 72°C for 1 minute, followed by a final extension step of 10 minutes at 72°C. Genotype was determined by direct sequencing using a CEQ™ DTCS-Quick Start Sequencing Kit and analyzed on a CEQ 8800 Genetic Analysis System (both Beckman Coulter, Brea, CA, USA).

Statistical analysis

Before data analysis, SNP data were examined for possible genotyping errors by assessing deviation from the Hardy–Weinberg equilibrium. Association of SULT1A1 activity with demographic (age and sex) and genetic (SNPs and copy number) variables was examined using analysis of variance with SAS software (v 9.2; SAS institute, Cary, NC, USA). The independent effects of functional SNPs and copy number were further assessed in analysis of variance and regression models adjusting for age and sex. Individual and collective effects of SNPs and copy number on SULT1A1 activity were assessed from partial sum square, R^2 , β -coefficient, and P value. In the regression model, the 638 G > A homozygous variant genotype was combined with heterozygous variant genotype due to small sample size and the combined group was treated as a referent. In addition, copy numbers ≥ 4 were combined in one category in the analysis. Statistical significance was set at $P < 0.05$ (two-sided) and all the statistical analyses were performed using SAS software.

Table 1 Primers for genotyping single nucleotide polymorphisms in the distal promoter of sulfotransferase isoform 1A1

Amplification primer	Sequence (5'-3')	Orientation
P1	cagtcgtggcttggagatc	Forward*
	gtcgggctctaagcggtg	Reverse
P2	atgttggtgtctgttggtcg	Forward*
	gtgtgtgggcagagtggaag	Reverse
P3	ctgtggagcctccttcaaac	Forward*
	acctgagctcttgggaacct	Reverse
P4	tgggtccgacaggtgtttac	Forward*
	ggaggctccacagacaagag	Reverse

Note: *Forward primers were used for sequencing.

Results

Mutation screening and allele frequency

We screened SNPs in the distal promoter of *SULT1A1* in 101 Japanese subjects and identified two common SNPs, –1975 G > C and –1135 G > A (the numbering of bases was designated relative to translation start site). We further characterized four common SNPs, –624 G > C, –396 A > G, –341 C > G, and –294 T > C, in the proximal promoter. Allele frequencies for –341 C > G were 0.5%, so we excluded this rare SNP from further analysis. We then genotyped for 902 A > G and 973 C > T in the 3'-UTR, 1307 G > A in the 3' flanking region, and *SULT1A1**1/2 in the coding region. The variant allele frequencies are shown in Table 2.

Association of *SULT1A1* SNPs in the promoter, 3'-UTR, and *SULT1A1**1/2 with platelet *SULT1A1* enzymatic activity

To investigate whether *SULT1A1* 3'-UTR SNPs can influence platelet *SULT1A1* enzymatic activity in Japanese subjects, we examined the association of individual SNPs with *SULT1A1* activity. In this population, 902 A > G, 973 C > T, and 1307 G > A were not associated with *SULT1A1* activity ($P > 0.05$, Table 2). Similarly, neither the SNPs in the proximal promoter (–624 G > C, –396 A > G, and –294 T > C) nor SNPs in the distal promoter (–1975 G > C and –1135 G > A) were associated with *SULT1A1* activity ($P > 0.05$, Table 2). However, *SULT1A1**1/2 was marginally associated with *SULT1A1* activity in Japanese subjects ($P = 0.037$). The *SULT1A1* activity in the AA/AG group was lower than that in the GG group (Figure 1). In addition, there was no significant difference in platelet *SULT1A1* enzymatic activity by sex or age in this population.

Table 2 Univariate analysis of demographic and genetic factors in relation to platelet sulfotransferase isoform 1A1 activity (nmol/min/mg protein) among Japanese subjects

Variable	rs number	Allele frequency	P
Age	NA	NA	0.22
Sex	NA	NA	0.54
–1975 G > C	rs9922110	0.366	0.22
–1135 G > A	rs2077412	0.381	0.87
–624 G > C	rs3760091	0.376	0.20
–396 A > G	rs750155	0.366	0.71
–294 T > C	rs4149382	0.490	0.56
902 A > G	rs6839	0.114	0.06
973 C > T	rs1042157	0.173	0.35
1307 G > A	rs4788068	0.198	0.75
638 G > A	rs9282861	0.109	0.037
Copy number	NA	NA	0.0009

Note: P values in bold were significantly different compared to Caucasians.

Abbreviation: NA, not applicable.

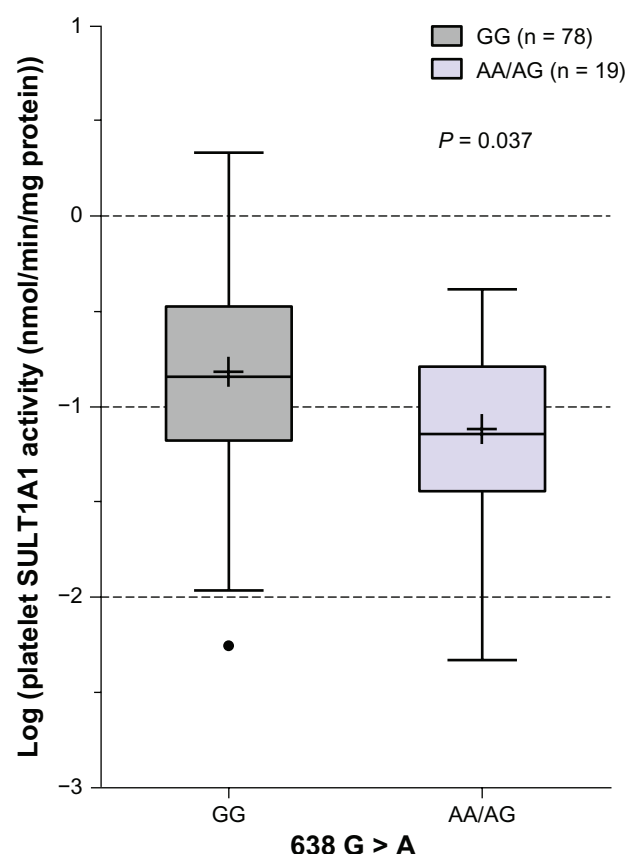


Figure 1 Box plot analysis of the association of *SULT1A1**1/2 (G638A) with platelet *SULT1A1* activity in Japanese subjects.

Notes: The plus sign and line inside each box indicate mean and median and the upper and lower limits of the box are the seventy-fifth and twenty-fifth percentiles, respectively. The vertical bars above and below show the maximum and minimum values, respectively. The solid circles outside the box are outlier values. Activity is presented in log scale. *P* values are shown for the genotypes whose differences in mean level of activity were statistically significant.

Abbreviation: *SULT1A1*, sulfotransferase isoform 1A1.

Copy number variation markedly influences *SULT1A1* activity in Japanese subjects

In the 97 Japanese subjects with genotype and phenotype data available, the frequency distribution of *SULT1A1* CNVs 2, 3, and ≥ 4 was 65.0%, 25.8%, and 9.2%, respectively. Notably, *SULT1A1* CNVs were significantly associated with platelet *SULT1A1* activity (trend test $P = 0.008$, Figure 2). Univariate analysis indicated that CNVs and the *SULT1A1**1 SNP were the only genetic variants tested that were significantly associated with activity in the Japanese population ($P = 0.0009$ and 0.037, respectively, Table 2). Pair-wise comparison indicated that *SULT1A1* activity is higher in subjects carrying higher copy numbers (3 or ≥ 4) than those with two copies of *SULT1A1* ($P = 0.005$ and $P = 0.025$, respectively). Copy number variation accounted for 10% of the observed variation in *SULT1A1* activity in Japanese subjects (Table 3).

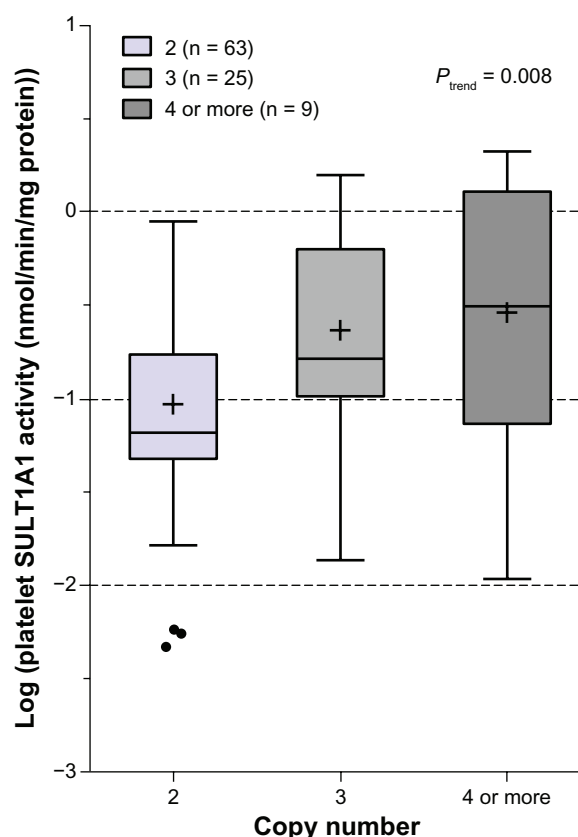


Figure 2 Box plot analysis of the association of *SULT1A1* copy number variant with platelet *SULT1A1* activity in Japanese subjects ($n = 97$).

Notes: Platelet *SULT1A1* activity was determined by colorimetric methods described in the “Materials, subjects, and methods” section and is shown in log scale. The P_{trend} test was performed for the three groups with different copies of the *SULT1A1* gene. The plus sign and line inside each box indicate mean and median and the upper and lower limits of the box are the seventy-fifth and twenty-fifth percentiles, respectively. The vertical bars above and below show the maximum and minimum values, respectively. The solid circles outside the box are outlier values. Activity is presented in log scale. *P* values are shown for the genotypes whose differences in mean level of activity were statistically significant.

Abbreviation: *SULT1A1*, sulfotransferase isoform 1A1.

Discussion

Genetic variation in *SULT1A1* is associated with functional effects on enzymatic activity, thermal stability, cellular phenotype, and protein degradation.^{7,23,24} Associations of genotype with phenotype have only been reported for Caucasian and African-American populations, with the magnitude of effect varying by ethnicity.⁸ For this reason, we sought to determine the impact of these genetic variants on enzymatic activity in an Asian population. We genotyped two SNPs in the *SULT1A1* distal promoter, four SNPs in the proximal promoter, two SNPs in the 3′-UTR, one SNP in the 3′ flanking region, and *SULT1A1**1/2 in the coding region. The correlation of SNPs, as well as copy number variation, with variation of *SULT1A1* platelet enzymatic activity in Japanese subjects was investigated.

*SULT1A1**1/2 has been reported to have frequencies of 0.332, 0.294, and 0.080 in Caucasian, African-American, and

Table 3 Results of multivariate analysis of variance and linear regression of platelet sulfotransferase isoform 1A1 (SULT1A1) activity (nmol/min/mg protein) with genetic predictors among Japanese subjects^a

Variable	n (%)	Partial sum of square	Partial R ²	β coefficient ^b	P
638 G > A (rs9282861)					
GG	78 (80.4)			1.21	0.17
AA/AG	19 (19.6)	1.19	0.04	1.00 ^c	
Copy number					
2	63 (65)			0.64	0.02
3	25 (25.8)			0.91	0.65
≥ 4	9 (9.2)	3.07	0.10	1.00 ^c	
Total model SS		29.76			

Notes: ^aModels with natural log of SULT1A1 activity as dependent variable and adjusted for demographics; ^bcoefficient transformed back to original scale; ^creference category. Bold text indicates the significance of the association with phenotype.

Abbreviation: SS, sum of square.

Han Chinese subjects, respectively.²⁵ In this study, the allele frequency for *SULT1A1**1/2 in Japanese subjects was 0.109, which is consistent with previous reports.^{13,26,27} Further, genotype–phenotype analysis indicated that *SULT1A1**1/2 was only marginally associated with SULT1A1 activity in Japanese subjects, accounting for only 4% of the observed inter-individual variability.

While promoter SNPs have been demonstrated to be significantly associated with enzymatic activity in Caucasians and African-Americans,¹⁹ we found no significant associations in Japanese subjects. We further identified two common SNPs in the distal promoter; similarly, these SNPs were not associated with platelet SULT1A1 activity.

We have reported that 3'-UTR SNPs play a central role in the regulation of SULT1A1 activity in both Caucasians and African-Americans and, combined with CNV, they account for the largest percentage of variability in enzymatic activity.²⁰ In this study, the allele frequencies of SNPs in the 3'-UTR were substantially lower than the allele frequencies in Caucasians and African-Americans and no influence on enzymatic activity was evident. Since the allele frequencies were low in Japanese subjects, it is possible that a larger study population could identify significant associations.

SULT1A1 CNVs also display ethnic differences, with 5% of Caucasian subjects possessing a single copy of the gene, 61% with two copies, and 26% with three or more copies, while 63% of African-American subjects had three or more copies.²⁸ This study further documented that the variability in the level of the SULT1A1 enzyme in platelet and liver samples was best explained by gene copy-number differences. In the present study, 65% of the

Japanese subjects had two copies of *SULT1A1*, which was similar to the distribution in Caucasians. Of all the genetic variants examined in the study, copy number variation has the greatest impact on SULT1A1 enzymatic activity in Japanese people, accounting for 10% of the observed inter-individual variability. Although the effects of copy number variation are statistically significant, the overall impact is small, leading to the speculation that environmental influences could be the greatest determinant of variability in SULT1A1 activity. Indeed, some dietary chemicals and environmental phenolic contaminants have been shown to be potent inhibitors of SULT1A1.^{29,30} Thus, studies of gene–environment interactions in determining SULT1A1 activity warrant further study in all ethnicities.

Conclusion

We found that *SULT1A1* CNVs and, to a lesser extent, *SULT1A1**1/2, were significantly associated with the SULT1A1 phenotype, while other genetic variants were not. The small magnitude of the contribution of these variants to inter-individual differences in phenotype in Japanese people indicates that results of pharmacogenomic and molecular epidemiological studies involving *SULT1A1* genetic variants should be interpreted with caution. Studies of other genetic, epigenetic, and environmental influences on SULT1A1 activity are required to fully understand inter-individual variability in this important enzyme.

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Disclosure

The authors declare no conflicts of interest in this work.

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