

Sulfotransferase gene copy number variation: pharmacogenetics and function

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Abstract. Pharmacogenetics is the study of the role of inheritance in variation to drug response. Drug response phenotypes can vary from adverse drug reactions at one end of the spectrum to equally serious lack of the desired effect of drug therapy at the other. Many of the current important examples of pharmacogenetics involve inherited variation in drug metabolism. Sulfate conjugation catalyzed by cytosolic sulfotransferase (SULT) enzymes, particularly SULT1A1, is a major pathway for drug metabolism in humans. Pharmacogenetic studies of SULT1A1 began over a quarter of a century ago and have advanced from biochemical genetic experiments to include cDNA and gene cloning,

gene resequencing, and functional studies of the effects of single nucleotide polymorphisms (SNPs). SNP genotyping, in turn, led to the discovery of functionally important copy number variations (CNVs) in the *SULT1A1* gene. This review will briefly describe the evolution of our understanding of *SULT1A1* pharmacogenetics and CNV, as well as challenges involved in utilizing both SNP and CNV data in an attempt to predict SULT1A1 function. *SULT1A1* represents one example of the potential importance of CNV for the evolving disciplines of pharmacogenetics and pharmacogenomics.

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Human cytosolic sulfotransferase (SULT) enzymes catalyze the sulfate conjugation of many drugs, other xenobiotics, neurotransmitters, and hormones – especially steroid hormones. 3'-Phosphoadenosine 5'-phosphosulfate (PAPS) is the sulfate donor for reactions catalyzed by SULTs (Weinshilboum and Otterness, 1994; Falany, 1997). These reactions typically result in increased water solubility and enhanced urinary excretion of the conjugated substrate (Glatt and Meinel, 2004). In addition to the biological inactivation of substrates, the SO_3^- transferred by SULTs can also serve as a leaving group, resulting in the formation of an active,

potentially toxic or carcinogenic metabolite (Miller and Surh, 1994; Glatt, 2000a; Glatt and Meinel, 2004). Therefore, SULT enzymes play an important role in drug metabolism, in toxicology, and in chemical carcinogenesis. As a result, variation in the ability to catalyze these reactions could potentially result in altered drug efficacy as well as risk for adverse drug reactions or carcinogenesis.

Drug metabolism is often separated into Phase I (oxidation, reduction, and hydrolysis) and Phase II (conjugation) reactions (Weinshilboum, 2003). The role of copy number variations (CNVs) in the pharmacogenetics of a major class of enzymes that catalyze Phase I reactions, the cytochromes P450 (CYPs), is addressed elsewhere in this volume (Johansson and Ingelman-Sundberg, 2008). The SULT family of Phase II conjugating enzymes has, like the CYPs, been the subject of intense pharmacogenetic studies (Glatt, 2000b; Glatt et al., 2001; Coughtrie, 2002; Glatt and Meinel, 2004; Weinshilboum and Adjei, 2005; Nowell and Falany, 2006). They were designed to determine the contribution of inheritance to individual differences in response to drugs that undergo sulfation as well as the possible role of inherited variation in sulfate conjugation in disease risk. As described

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Table 1. List of the 13 human *SULT* genes with chromosomal band and physical locations indicated

Gene	Chromosome band	Physical location
<i>SULT1C2</i> ^a	2q12.3	108271527–108292803
<i>SULT1C3</i>	2q12.3	108230083–108248239
<i>SULT1C4</i>	2q12.3	108360853–108370702
<i>SULT6B1</i>	2p22.2	37248467–37269 194
<i>SULT1B1</i>	4q13.3	70627275–70661019
<i>SULT1E1</i> ^a	4q13.3	70741519–70760459
<i>SULT1A1</i> ^a	16p11.2	28524419–28528858
<i>SULT1A2</i> ^a	16p11.2	28510767–28515302
<i>SULT1A3</i> ^a	16p11.2	29378695–29383802
<i>SULT1A4</i> ^a	16p11.2	30118037–30123121
<i>SULT2A1</i> ^a	19q13.32	53065682–53081405
<i>SULT2B1</i> ^a	19q13.32	53747241–53794496
<i>SULT4A1</i>	22q13.2	42551720–42589711

^a Gene has undergone resequencing studies designed to identify and functionally characterize common polymorphisms (Her et al., 1996; Raftogianis et al., 1997, 1999; Freimuth et al., 2001; Thomae et al., 2002; Adjei et al., 2003; Thomae et al., 2003; Hildebrandt et al., 2004; Ji et al., 2007).

in subsequent paragraphs, sulfation pharmacogenetics initially involved studies of single nucleotide polymorphisms (SNPs), but we now know that we must also take copy number variations into consideration (Hebbring et al., 2007). The evolution of our understanding of *SULT* pharmacogenetics – particularly pharmacogenetics of the important drug- and hormone-metabolizing enzyme *SULT1A1* – illustrates the importance of including CNVs as a potential pharmacogenetic mechanism. This review will briefly describe the human *SULT* gene family, including the *SULT1A* subfamily that includes *SULT1A1*. The focus will then be placed on *SULT1A1*, a widely expressed isoform that plays an important role in the biotransformation of a large number of drugs and steroid hormones, especially estrogens. *SULT1A1* represents an excellent example of the challenges and the importance for pharmacogenetics of unifying SNP data, CNV data, and function.

The human *SULT* gene family

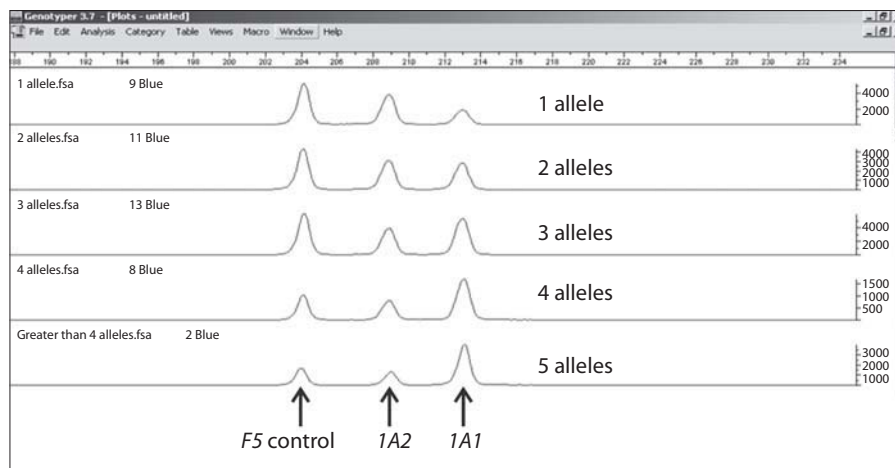
The human cytosolic *SULT* gene family includes 13 members (Table 1). These genes map to clusters on chromosomes 2, 4, 16, and 19, plus two single genes on chromosomes 2 and 22 (Blanchard et al., 2004; Freimuth et al., 2004). The chromosome 2 cluster includes *SULT1C2*, *1C3*, and *1C4*, all located within a 150-kb region at 2q12.3. Proteins encoded by *SULT1C* family members have been shown to catalyze the metabolic ‘activation’ of procarcinogens such as N-hydroxyl-2-acetylaminofluorene to form potent carcinogens (Glatt et al., 2000). The chromosome 4 *SULT* genes include *SULT1B1*, *1E1*, and *1D1*. These genes map to a 110-kb cluster at 4q13.3. *SULT1E1* was previously referred to as estrogen sulfotransferase since this isoform has the highest

affinity for estrogens of any member of the *SULT* family (Adjei and Weinshilboum, 2002). However, *SULT1A1* may play a more important role in overall estrogen sulfate conjugation than does *SULT1E1* because of its ubiquitous expression. *SULT1B1* has been reported to contribute to thyroid hormone sulfate conjugation (Wang et al., 1998), although there is evidence that other *SULT* isoforms can also catalyze that reaction (Glatt and Meinl, 2004). Genes encoding the two members of the human *SULT2* subfamily map to chromosome 19. These genes encode enzymes that metabolize steroids such as dehydroepiandrosterone, pregnenolone, and cholesterol (Falany, 1997). Because of their possible pharmacogenetic importance, many of the human *SULT* genes have been subjected to comprehensive gene resequencing, followed by functional genomic studies (Her et al., 1996; Raftogianis et al., 1997, 1999; Freimuth et al., 2001; Thomae et al., 2002, 2003; Adjei et al., 2003; Hildebrandt et al., 2004; Ji et al., 2007) (Table 1). The most intensively studied *SULT* genes are those in the *SULT1A* subfamily within a gene cluster at chromosome 16p11.2. *SULT1A1*, *1A2*, *1A3*, and *1A4* map to an area on the short arm of chromosome 16 in a region rich in repetitive sequences and segmental duplications (Hildebrandt et al., 2004; Bradley and Benner, 2005). The four enzymes encoded by these genes are highly homologous in their amino acid sequences. For example, *SULT1A3* and *1A4* are identical in sequence, *SULT1A1* and *1A2* are 96% identical, and *SULT1A1* and *1A3/1A4* are 93% identical in amino acid sequence (Raftogianis et al., 1996; Hildebrandt et al., 2004). *SULT1A1* is widely expressed in a variety of human tissues and plays an important role in the biotransformation of a large number of drugs and of estrogen hormones (Adjei and Weinshilboum, 2002; Coughtrie, 2002; Glatt and Meinl, 2004), but with lower affinity than *SULT1E1* (Adjei et al., 2003). *SULT1A2* is not widely expressed (Coughtrie, 2002; Nowell et al., 2005), while *SULT1A3* and *1A4*, both of which encode and transcribe active proteins (Wood et al., 1994; Hildebrandt et al., 2004), catalyze the biotransformation of catecholamine neurotransmitters such as dopamine and norepinephrine (Glatt and Meinl, 2004). The structures of *SULT1A3* and *1A4* illustrate the fact that large segmental duplications occur in this area of chromosome 16. These genes, with virtually identical sequences, are contained within two 146-kb duplicated segments, separated by 728 kb of DNA (Hildebrandt et al., 2004). Because it is so widely expressed and because it plays such a critical role in drug metabolism, *SULT1A1* has been the most intensively studied of the *SULT* isoforms, both from a biochemical and a pharmacogenetic perspective.

SULT1A1 pharmacogenetics

Pharmacogenetic studies of *SULT1A1* focused initially on SNPs, both non-synonymous and functional promoter SNPs of the gene that influence transcription (Prondzinski et al., 2003; Buckland et al., 2005; Hebbring et al., 2007). The association of those SNPs with function, although clearly

Fig. 1. Quantitative fluorescent-based PCR assay. The figure shows peaks for the controls, Coagulation Factor V (*F5*) and *SULT1A2*, as well as peaks for 1–5 copies of *SULT1A1* (Hebbring et al., 2007, with the permission of *Human Molecular Genetics*).



defined during in vitro studies (Prondzinski et al., 2003), did not always correlate well with in vivo function (Raftogianis et al., 1997; Glatt and Meinel, 2004). Therefore, the recent discovery of functionally important *SULT1A1* CNVs (Hebbring et al., 2007) – when combined with SNP data – may enhance our understanding of *SULT1A1* pharmacogenetics. Pharmacogenetic studies of *SULT1A1* also illustrate, as described subsequently, the practical difficulty of interpreting SNP genotypes in conjunction with CNV data. Subsequent paragraphs will briefly describe the discovery and characterization of *SULT1A1* SNPs and their role in the ensuing discovery of CNVs for this important gene, followed by a description of attempts to interpret the functional effects of *SULT1A1* SNPs together with CNVs to help make it possible to correlate genotypic data with function.

Studies of the genetic regulation of human *SULT1A1* began long before either the cDNA or gene encoding this enzyme had been cloned and characterized. Biochemical genetic studies performed in the 1980s using human blood platelets (an easily obtained tissue in which the enzyme is expressed) determined that inheritance played a major role in the variation of two phenotypes, level of enzyme activity and enzyme thermal stability (Van Loon and Weinshilboum, 1984; Campbell et al., 1987; Anderson et al., 1988; Price et al., 1989). The decade of the 1990s witnessed the cloning and characterization of the human *SULT1A1* cDNA and gene (Wood et al., 1994; Aksoy and Weinshilboum, 1995; Raftogianis et al., 1996), followed quickly by resequencing of the gene's coding region using 150 DNA samples from Caucasian subjects (Raftogianis et al., 1997). Two common non-synonymous SNPs were observed, *SULT1A1**2 (rs9282861, G638A, Arg213His) and *SULT1A1**3 (rs1801030, A667G, Met223Val). The *SULT1A1**2 variant was the most common of the two, with a minor allele frequency (MAF) of 31–33% in Caucasian subjects while *SULT1A1**3 had a MAF of ~1% in these subjects (Carlini et al., 2001). As we have now learned to expect, there were striking differences among ethnic groups in allele frequencies, with *SULT1A1**2 having a frequency of only 8% and *SULT1A1**3 a frequency of 0.6% in Han Chi-

nese subjects. However, *SULT1A1**3 had a frequency of 23% in African-American subjects (Carlini et al., 2001). We will see subsequently that ethnic variation in frequency also occurs with *SULT1A1* CNVs. The *SULT1A1**2 allele was associated with a substantial decrease in levels of both enzyme activity and thermostability (Raftogianis et al., 1997) as a result, in part, of altered degradation of that variant allozyme (Raftogianis et al., 1999). Subsequently, two SNPs in the promoter of *SULT1A1* were reported to influence transcription (Prondzinski et al., 2003; Hebbring et al., 2007). Therefore, three SNPs, *1A1**2 (rs9282861) and two promoter SNPs (rs3760091 and rs750155), have been the subject of a series of molecular epidemiology studies that often resulted in equivocal or inconclusive results (Glatt and Meinel, 2004). However, it was observations made in the course of genotyping those three SNPs which led to the discovery that *SULT1A1* also displayed functionally significant CNVs.

***SULT1A1* CNVs**

When *SULT1A1* genotyping was performed using the semi-quantitative pyrosequencing assay, an unusual peak distribution for the *SULT1A1**2 polymorphism was observed. After confounding artifacts were eliminated as the cause, it seemed possible that these observations might be due to CNVs. Therefore, a quantitative fluorescent-based PCR assay was designed in which both *SULT1A2* and the Coagulation Factor V (*F5*) genes were used as controls to which *SULT1A1* gene amplification could be compared. When that assay was applied, the results were compatible with the conclusion that one to five copies of *SULT1A1* were present in individual DNA samples (Fig. 1). This PCR-based assay was then used to study a series of DNA samples obtained from human liver surgical biopsy samples as well as from the Coriell Cell Repository. The results of those studies were also compatible with the existence of *SULT1A1* CNVs, with striking frequency differences between Caucasian-American (CA) and African-American (AA) subjects (Fig. 2). For example, 4.7% of CA subjects appeared to have

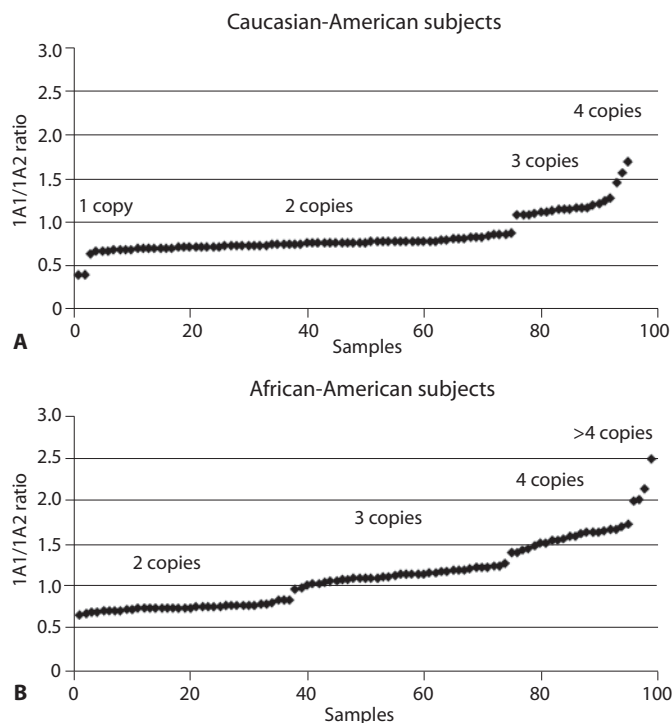


Fig. 2. Peak height ratios of *SULT1A1* to *SULT1A2* for 100 DNA samples from both (A) Caucasian-American and (B) African-American subjects graphed to indicate *SULT1A1* copy numbers (Hebbring et al., 2007, with the permission of *Human Molecular Genetics*).

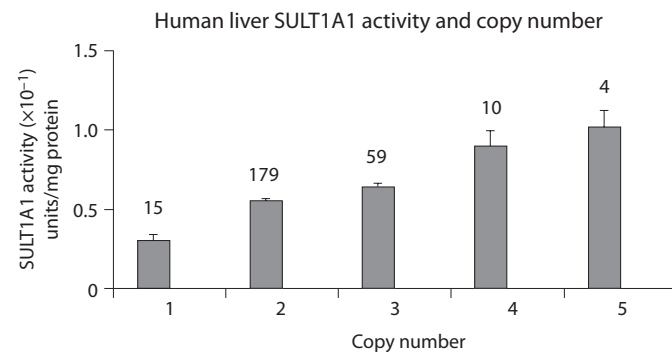


Fig. 3. Plot of *SULT1A1* enzymatic activity in 267 human liver biopsy samples as a function of *SULT1A1* copy number. The values above the bar represent the number of samples tested in each group (Hebbring et al., 2007, with the permission of *Human Molecular Genetics*).

only one copy of *SULT1A1* in their genome, while 25.7% had three or more copies. However, none of the 100 AA subjects studied had only a single copy of the gene, but 62.6% had three or more.

Furthermore, when *SULT1A1* copy number was correlated with the results of a *SULT1A1*-specific radiochemical enzymatic assay performed using cell lysates from 267 human liver samples, CNV correlated well with enzyme activity (Fig. 3). However, the functional SNPs that had been assayed in a large number of molecular epidemiology studies

Table 2. The table lists genotype frequencies (in %) for the two *SULT1A1* promoter SNPs (rs3760091 and rs750155), and the non-synonymous SNP (Arg213His, rs9282861) with respect to copy number in 761 randomly selected Caucasian women. The 'A' allele represents C for all SNPs, while 'B' represents the G allele in rs3760091 and T in rs750155 and rs9282861.

Genotype	<i>SULT1A1</i> promoter SNPs		<i>SULT1A1</i> *2
	rs3760091	rs750155	rs9282861
A	1.8	2.1	2.7
B	1.8	1.6	1.2
AA	24.9	16.0	22.3
AB	31.9	32.3	31.0
BB	7.7	15.8	11.0
AAA	5.4	3.6	12.7
AAB	7.0	9.2	9.4
BAA	8.8	8.8	2.8
BBB	4.2	3.9	0.4
AAAA	0.9	0.7	3.6
AAAB	1.2	1.7	1.3
AABB	1.8	1.9	1.3
BAAA	1.6	1.5	0.0
BBBB	0.9	1.1	0.3

over the past decade (over 100 such studies were listed by PubMed after search with the term '*SULT1A1* polymorphism') showed little correlation when CNV was taken into consideration (Hebbring et al., 2007). In summary, this series of experiments suggested that both SNP genotype and CNV need to be determined in order to correlate *SULT1A1* genotype with clinically and biologically relevant phenotypes. However, assessing *SULT1A1* SNP genotype presents a challenge in the presence of CNVs. That is true because many SNP genotyping methods can not reliably detect an imbalance between two SNP alleles. When those techniques are used, it can be determined whether a sample is homozygous or heterozygous, but when more than two alleles are present, the number of each allele can not be resolved. In order to assay for allele 'dosage', techniques such as pyrosequencing are required to determine the ratio between signals from the two alleles. For example, when pyrosequencing is utilized, allele ratios can be used, together with copy number genotype, to determine how many copies of each allele are present. That can be accomplished by plotting 'percent signal' for each allele, separated into groups on the basis of copy number. Plots of the data can then be analyzed to assess the number of copies of each allele present. For example, if a sample has a copy number of three, and the pyrosequencing peak height ratio is 66.6% G and 33.4% C, that sample would have two alleles with G and one allele with C at the locus of interest. In our experience, it is easiest to assess SNP allele dosage if the SNP data are grouped by odd or even copy numbers, as shown in Fig. 4. In that figure, the 'even copy number' plot shows that alleles with either two or four copies are identical with regard to SNP genotype when half of the alleles are of one type and half of the other, i.e., ~0.5 on the '% allele' axis (1 of 2 or 2 of 4). Furthermore, compound het-

erozygotes (1 of 4) for subjects carrying four copies can be easily identified with this type of plot, i.e., they are all at either 0.25 or 0.75 on the Y-axis. Perhaps even more striking, compound heterozygotes can be easily separated in plots for samples that carry an odd number of *SULT1A1* copies (one or three copies). This type of visual depiction makes it possible to easily add SNP allele ‘calls’ to copy number data (Fig. 4B). When we used this approach to genotype DNA samples from 761 randomly selected Caucasian women for the three common *SULT1A1* functional SNPs (two in the gene promoter and the *SULT1A1*2* non-synonymous SNP), we observed every possible combination of SNP genotypes for the duplicated alleles (Table 2). This observation contrasts with the situation for the functionally and clinically relevant cytochrome P450 gene *CYP2D6*, a gene that has also undergone deletion and duplication in the course of evolution (Johansson et al., 1993; Dalen et al., 1998; Johansson and Ingelman-Sundberg, 2008). When multiple copies of *CYP2D6* are present, they generally involve only a single duplicated allele, not the variety of combinations that we observed for *SULT1A1* (Table 2). This difference probably results from different mechanisms by which CNVs evolved.

Conclusion

Pharmacogenetics has been heralded as one of the major applications of genomics to help ‘individualize’ 21st century medicine. The initial focus of pharmacogenetics has understandably been on SNPs. However, the examples provided by *SULT1A1* and *CYP2D6* (Johansson and Ingelman-Sundberg, 2008) make it clear that both SNPs and CNVs may need to be taken into account to successfully link genotypic variation to variation in drug response phenotypes. Once techniques are developed that make this process efficient, accurate, and cost effective, there can be little doubt that

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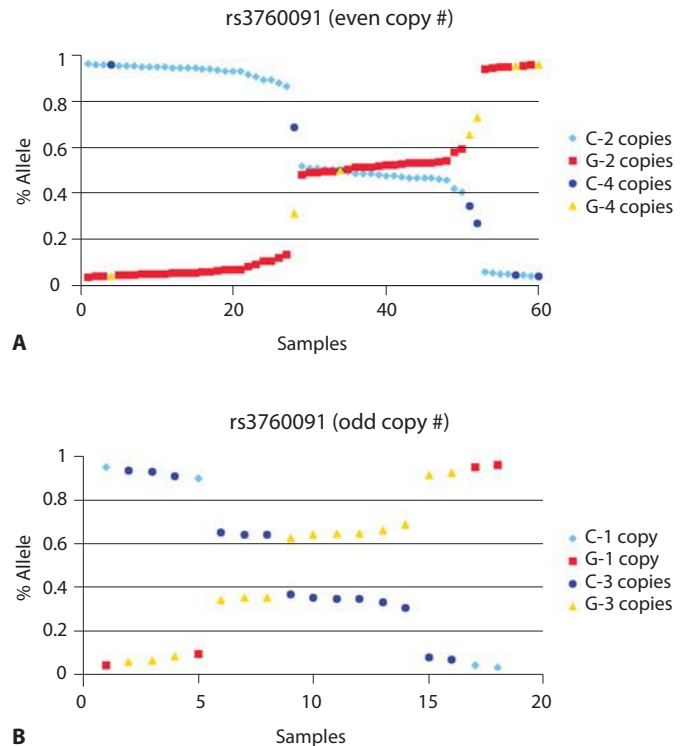


Fig. 4. Plot of *SULT1A1* SNP data sorted by ‘% allele’ from pyrosequencing data for each sample. (A) Samples having an even number of copies of *SULT1A1* (2 and 4). (B) Samples having an odd number of copies (1 and 3).

both the ‘discovery phase’ of pharmacogenetics and pharmacogenetic clinical assays will – when appropriate – routinely obtain both CNV data and SNP genotyping, as described here for *SULT1A1*, to help make it possible to better individualize drug therapy.

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