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SHORT COMMUNICATION

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Analyses of 5′ regulatory region polymorphisms in human *SLC22A6* (*OAT1*) and *SLC22A8* (*OAT3*)

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Abstract Kidney excretion of numerous organic anionic drugs and endogenous metabolites is carried out by a family of multispecific organic anion transporters (OATs). Two closely related transporters, *SLC22A6*, initially identified by us as *NKT* and also known as *OAT1*, and *SLC22A8*, also known as *OAT3* and *ROCT*, are thought to mediate the initial steps in the transport of organic anionic drugs between the blood and proximal tubule cells of the kidney. Coding region polymorphisms in these genes are infrequent and pairing of these genes in the genome suggests they may be coordinately regulated. Hence, 5′ regulatory regions of these genes may be important factors in human variation in organic anionic drug handling. We have analyzed novel single nucleotide polymorphisms in the evolutionarily conserved 5′ regulatory regions of the *SLC22A6* and *SLC22A8* genes (phylogenetic footprints) in an ethnically diverse sample of 96 individuals (192 haploid genomes). Only one polymorphism was found in the *SLC22A6* 5′ regulatory region. In contrast, seven polymorphisms were found in the *SLC22A8* 5′ regulatory region, two of which were common to all ethnic groups studied. Computational analysis permitted phase and haplotype reconstruction. Proximity of these non-coding polymorphisms to transcriptional regulatory elements (including potential sex steroid response elements) suggests a potential influence on the level of transcription of the *SLC22A6* and/or *SLC22A8* genes and will help define their role in variation in human drug, metabolite and toxin excretion. The clustering of *OAT* genes in the genome raises the possibility that nucleotide polymorphisms in *SLC22A6* could also effect *SLC22A8* expression, and vice versa.

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Introduction

The organic anion transporters (OATs) constitute a subfamily within the *SLC22* family of solute carriers (Eraly et al. 2003). Two members of this subfamily, *SLC22A6* (also known as *OAT1*), originally identified as novel kidney transporter (NKT; Lopez-Nieto et al. 1996, 1997) and *SLC22A8* (also known as *OAT3*), originally identified as reduced in osterosclerosis (ROCT) (Brady et al. 1999), function as the major basolateral transporters of a wide variety of drugs and toxins excreted via the proximal tubule of the kidney. These drugs include nonsteroidal anti-inflammatory drugs, antibiotics, antivirals (such as adefovir and cidofovir), antihypertensives, diuretics, methotrexate and many other commonly prescribed drugs (Eraly et al. 2004a, b). They are also responsible for the excretion of toxins such as Ochratoxin A and mercurials, and are believed to be essential for the mediation of the renal toxicity of these agents (Sweet 2005). In addition, recent mouse knockout studies suggest that these two genes are sufficient to explain most of the excretion of certain prototypical organic anions like para-aminohippurate (PAH), estrone sulfate and taurocholate (Sweet et al. 2002; Eraly et al. 2005), consistent with the notion that these two genes mediate the rate-limiting step for uptake of organic anion drugs from the blood.

For these reasons, there has been much interest in the possibility that polymorphisms in *SLC22A6* and *SLC22A8* may be partly responsible for variation in the handling and efficacy of the many commonly used drugs that are transported by these transporters. Likewise, such polymorphisms could conceivably explain susceptibility to the toxicity of drugs and environmental toxins. Recent studies have thus analyzed coding region

polymorphisms in these genes (Xu et al. 2005; Bleasby et al. 2005; Fujita et al. 2005). However, unlike other members of this subfamily such as *SLC22A11* (also known as *OAT4*) and *SLC22A12* (also known as *URAT1* and originally identified as *RST* in mouse), there appear to be relatively infrequent nonsynonymous coding region human polymorphisms in *SLC22A6* and *SLC22A8* (Xu et al. 2005). Thus, while some variation in drug/toxin handling might be explained by coding region polymorphisms in these genes, the apparent paucity of such polymorphisms suggests the need to also analyze noncoding region variation in these genes, which might, for example, affect the transcription of *SLC22A6* and *SLC22A8* and thereby the total levels of functional protein.

SLC22A6 and *SLC22A8* exist as a tandem pair on human chromosome 11 (Fig. 1). Given the complex genomic structure and the as yet undetermined promoter regions of *SLC22A6* and *SLC22A8*, we have utilized the computational technique of phylogenetic footprinting to identify evolutionarily conserved noncoding regions of the *SLC22A6* and *SLC22A8* genes (Fig. 1); these regions are likely to contain sequences important for regulating gene expression (Kim et al. 2004; Prohaska et al. 2004). We identified three such regions in the *SLC22A6* gene and five regions in the *SLC22A8* gene. We then sequenced these regions in an ethnically diverse panel of human DNA samples in order to identify single nucleotide polymorphisms (SNPs) likely to affect the expression of the *SLC22A6* and *SLC22A8* transcripts. The data suggest a number of polymorphisms that could affect *SLC22A8* expression and a more limited number that could affect *SLC22A6* expression. This approach can be more broadly applied to identify potential regulatory region SNPs for *SLC22A6* and *SLC22A8*, as well as other *SLC22* family members. It will be important to consider these polymorphisms, along with those found in coding regions, in clinical studies aimed at understanding variation in drug handling and toxin susceptibility mediated via OATs.

Materials and methods

Phylogenetic footprinting

We have previously defined phylogenetic footprints (PFs) of *SLC22A6* and *SLC22A8* 5′ regulatory regions (Eraly et al. 2003). Briefly, reference *SLC22A6* and *SLC22A8* regulatory sequences for human, chimpanzee and mouse were acquired from the University of California Santa Cruz (UCSC) Genome Browser (http://www.genome.ucsc.edu/). An 8 kb region of sequence upstream from the first translational start site for the *SLC22A6* and *SLC22A8* genes was obtained for each species (Fig. 1). PFs were then identified through sequence alignment using pairwise BLAST (http://www.ncbi.nlm.nih.gov/BLAST) and then realigned using ClustalX (http://bips.u-strasbg.fr/fr/Documentation/ClustalX/). Homology between human, chimpanzee, and mouse was confined to three regions on the promoter/enhancer of *SLC22A6* (designated PFi1, PFi2, and PFi3) and five regions on the promoter/enhancer of *SLC22A8* (designated PFu1 to PFu5). PFi1, PFi2, and

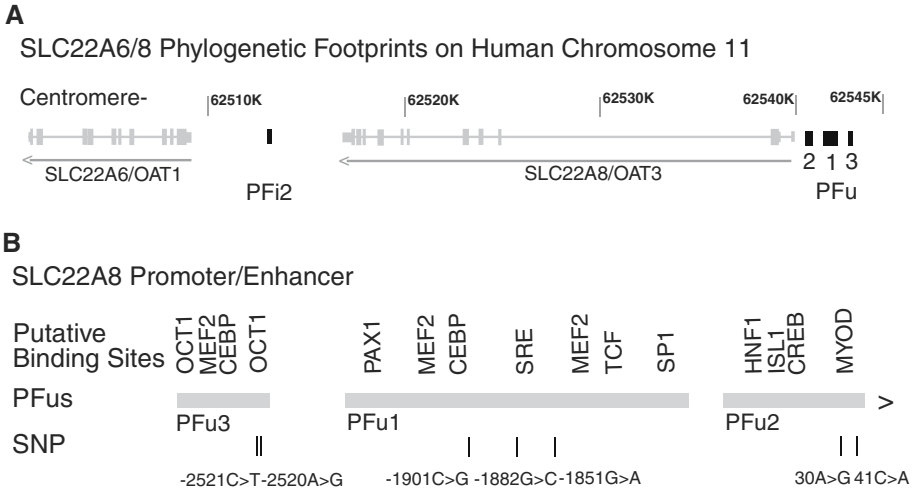

Fig. 1a,b Locations of single nucleotide polymorphisms (SNPs) on phylogenetic footprints (PFs) of human *SLC22A6* and *SLC22A8* on chromosome 11. **a** Locations of *SLC22A6* and *SLC22A8* on human chromosome 11. The genomic distance is relative to the centromere, derived from the University of California Santa Cruz (UCSC) genome database. *SLC22A6* and *SLC22A8* are separated by a small interval of 8 kb, and the direction of their transcription is indicated by *arrows*. The proximal locations of the evolutionarily conserved regulatory regions of PFs are indicated relative to the transcriptional start sites. The locations of the PFs are relative to each other, and the distances between them are not proportional. **b** Conserved regions on the promoter/enhancer *SLC22A8* (PFus) are depicted relative to the transcription start site (*arrow*). Selected putative transcription factor sites are listed according to general localization on the PFus. Positions of the SNPs, by distance to the transcription start site, are marked to indicate the proximity to the transcription factor binding sites

PFi3 started at −239, −3,700, and −7,600 base pairs (bp) upstream from the *SLC22A6* transcription start site. PFu1, PFu2, PFu3, PFu4, and PFu5 started at −2,055, −147, −2,608, −6,800, and −3,500 bp upstream from the *SLC22A8* transcription start site.

SNP detection

Ninety-six DNA samples, 52 of which were from females and 44 from males, representative of a generally healthy population and chosen from 11 ethnic groups, were obtained from the Coriell panel. PCR primers encompassing the PF of human *SLC22A6* and *SLC22A8* genes were designed using Primer3 (http://www-genome.wi.mit.edu/cgi-bin/primer/primer3.cgi). PF sequences were amplified by PCR from 16 ng DNA in a final volume of 20 µl. Residual primers were removed by treatment with exonuclease 1 and shrimp alkaline phosphatase. Sequencing was performed on an ABI3100 automated sequencer with BigDye terminators (Applied Biosystems, Foster City, CA), and analyzed using the Phred/Phrap/Consed suite of software to arrive at base quality scores (http://www.phrap.org). Polymorphisms and heterozygosity were located using Polyphred and were then also manually confirmed.

Haplotype determination

Genotypes were created for each individual and haplotypes were inferred using PHASE 2.1.1 (http://www.stat.washington.edu/stephens/software.html). PHASE employs an algorithm that partitions each locus into segments and then creates statistically probable haplotypes for each individual; haplotype frequencies are then determined for the population and extrapolated to a population of 10,000 in order to satisfy the requirement of the algorithm. To discern the phylogenetic lineage of each haplotype, a network was created using the software package ARLEQUIN (http://anthro.unige.ch/arlequin/). This network also incorporates the extrapolated haplotypes inferred by PHASE from a larger population size.

Results and discussion

SNP detection

SLC22A6 (OAT1)

An A to G substitution was identified on one of the conserved portions of the *SLC22A6* 5′ regulatory region (Pfi2), −3,655 bp from the transcription start site of *SLC22A6* (Table 1). This SNP was located 8 bp downstream from the consensus Wilm's tumor gene (*WT1*) recognition site, a gene critical for the development of a functional kidney. This polymorphism was found in a

Table 1 Human SLC22A6 (OAT1) and SLC22A8 (OAT3) 5′ regulatory region single nucleotide polymorphisms. SNP frequency is given by ethnic group and total population (96 individuals, 192 Alleles). *N** Nucleotide substitution, *PFi* phylogenetic footprints for *SLC22A6*, *PFu* phylogenetic footprints for *SLC22A8*, *WT* wild type or major allele as listed in University of California Santa Cruz (UCSC) Genome Browser (http://www.genome.ucsc.edu), *SNP* minor allele or newly detected single nucleotide polymorphism

Base-pairs from translation Start Site	5′ Regulatory region	5′ flanking * N * 3′ flanking	Chinese (20)	Indo-Pakistani (18)	Japanese (20)	SE Asian (20)	South American (Andean) (20)	South Saharan African (18)	Ashkenazi Jewish (20)	Northern Saharan African (14)	Pacific Islander (14)	SW American (Mexican) (10)	Northern European (18)	Total population (192)
SLC22A6 (OAT1)														
−3,655	PFi 2 WT	CATGAG G GCACCA	1	1	1	1	1	1	1	1	0.928	1	1	0.995
	PFi 2 SNP	CATGAG A GCACCA	0	0	0	0	0	0	0	0	0.072	0	0	0.005
SLC22A8 (OAT3)														
−1,901	PFu1 WT	TAGGAA C CAGAAA	1	1	1	0.950	1	1	1	1	1	1	1	0.995
	PFu1 SNP	TAGGAA G CAGAAA	0	0	0	0.050	0	0	0	0	0	0	0	0.005
−1,882	PFu1 WT	AAGAGG G CAAATG	0.450	0.445	0.700	0.400	0.450	0.444	0.900	0.357	0.643	0.400	0.555	0.531
	Pfu1 SNP	AAGAGG C CAAATG	0.550	0.555	0.300	0.600	0.550	0.556	0.100	0.643	0.357	0.600	0.445	0.469
−1,851	PFu1 WT	CAGGGC G GCAGC	0.800	0.778	0.650	0.800	0.850	0.778	0.650	0.929	0.929	0.800	0.889	0.797
	PPu1 SNP	CAGGGC A GCAGC	0.200	0.222	0.350	0.200	0.150	0.222	0.350	0.071	0.071	0.200	0.111	0.203
30	PFu2 WT	CCTACT A CAGCAG	1	1	1	0.950	1	1	1	1	1	1	1	0.995
	PFu2 SNP	CCTACT G CAGCAG	0	0	0	0.050	0	0	0	0	0	0	0	0.005
41	PFu2 WT	AGCTGC C GGCCCC	1	1	0.950	1	1	1	1	1	1	1	1	0.995
	PFu2 SNP	AGCTGC A GGCCCC	0	0	0.050	0	0	0	0	0	0	0	0	0.005
−2,521	PFu3 WT	TTTGAA C ATATTG	1	1	1	1	0.950	1	1	1	1	1	1	0.995
	Pfu3 SNP	TTTGAA T ATATTG	0	0	0	0	0.050	0	0	0	0	0	0	0.005
−2,520	PFu3 WT	TTGAAC A TATTGA	1	1	1	1	1	0.945	1	1	1	1	1	0.995
	PFu3 SNP	TTGAAC G TATTGA	0	0	0	0	0	0.055	0	0	0	0	0	0.005

single individual of Pacific Islander descent (minor allele frequency 0.07 in the Pacific Islander sample, or 0.005 in the total population sample).

SLC22A8 (OAT3)

There were seven SNPs located on the PFs of *SLC22A8* (Table 1). Three of these SNPs were found on PFu1. The first SNP (C to G) was found at position −1,901 in an individual of Southeast Asian descent (minor allele frequency 0.05 in the Southeast Asian sample, 0.005 in the total sample). A second SNP (G to C substitution) at position −1,882 was common to all ethnic groups studied (minor allele frequency ranging from 0.10 to 0.64 within specific populations and 0.47 for the total sample). A third SNP (G to A) at −1,851 was also found in all ethnic groups (minor allele frequency within groups ranging from 0.07 to 0.35 and a minor allele frequency of 0.20 in total population). Of note, G1882C and G1851A are located 8 bp upstream and 5 bp downstream, respectively, of the consensus steroid hormone recognition element (SRE).

There were two SNPs located on PFu2 of *SLC22A8* (Fig. 1b). The first was an A to G substitution, located 30 bp downstream from the *SLC22A8* transcription start site in an individual of Southeast Asian origin (minor allele frequency 0.05, 0.005 overall). The second SNP, a C to A substitution, was found 41 bp downstream in an individual of Japanese descent (Table 1).

Two SNPs were found on PFu3 of *SLC22A8* (Fig. 1b). The first was a C to T substitution at position −2,521, found in an individual of the South American Andean gene pool (minor allele frequency of 0.05, 0.005 overall). The second SNP on PFu3 region was an A to G substitution at position −2,520 in an individual of South Saharan African decent (Table 1).

Haplotype determination

There was primarily one *SLC22A6* 5′ regulatory region haplotype, identical to the chimpanzee sequence for this region. The majority of *SLC22A8* 5′ regulatory region haplotypes had one of the three-nucleotide sequences at these positions −2,521, −2,520, −1,901, −1,882, −1,851, 30, and 41: CACCGAC (haplotype 1); CACGGAC (haplotype 2); or CACGAAC (haplotype 3) (Fig. 2). The major human *SLC22A8* haplotype (haplotype 1) appeared to be derived from the chimpanzee/ancestral haplotype (haplotype 2).

These analyses have focused on evolutionarily conserved *SLC22A6* and *SLC22A8* 5′ regulatory regions (phylogenetic footprints designated as Pfis and Pfus, respectively) in order to identify SNPs that could potentially alter the expression of *SLC22A6* and *SLC22A8* (Fig. 1). With the exception of a G to C transversion at −1,882 (rs11231306) on the *SLC22A8* 5′ regulatory region, the SNPs identified in this study are novel. Only one polymorphism was found on the *SLC22A6* 5′ regulatory region, suggesting that transcription of this gene is highly conserved. In contrast, seven polymorphisms were found on the *SLC22A8* 5′ regulatory region, two of which were present among all ethnic groups studied, suggesting increased nucleotide diversity in the *SLC22A8* 5′ regulatory region (nucleotide diversity of 0.012) compared to that in the 5′ regulatory region of *SLC22A6* (nucleotide diversity of 0.006) (Fig. 1).

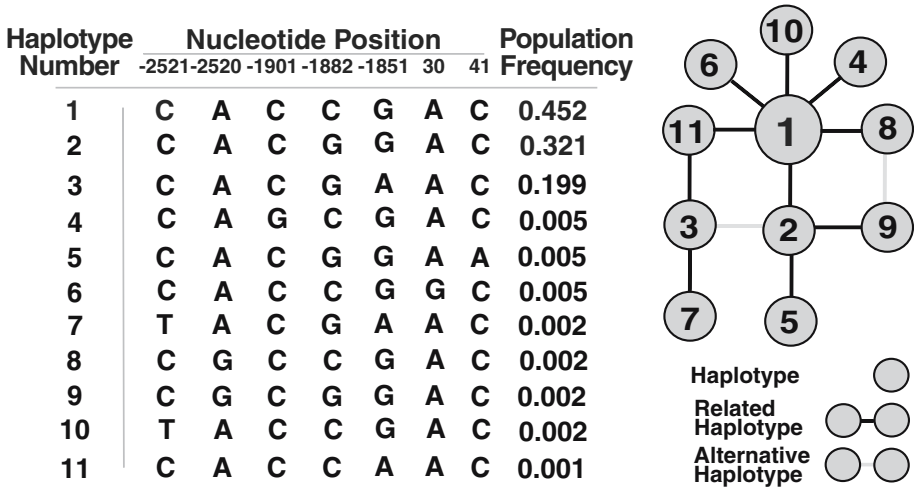

Fig. 2 *SLC22A8* 5′ regulatory region haplotypes. Haplotypes were inferred using PHASE 2.1.1 (http://www.stat.washington.edu/stephens/software.html). Haplotype networks were generated by ARLEQUIN. Each *circle* represents the corresponding haplotype number. Haplotypes that are directly related and have a relationship of one (a single nucleotide difference) are connected with *one solid line*. *Dashed lines* symbolize alternate relationships. The major human *SLC22A6* 5′ regulatory region haplotype is the same as the chimpanzee/ancestral haplotype (not shown). There are 11 potential human *SLC22A8* 5′ regulatory region haplotypes; however, over 95% of human *SLC22A8* 5′ regulatory region haplotypes are either haplotype 1, 2 or 3. The major human *SLC22A8* 5′ regulatory region haplotype (haplotype 1) appears to have been derived from the chimpanzee/ancestral haplotype (haplotype 2)

The most common *SLC22A8* regulatory region haplotype (haplotype 1 from Fig. 2) appears to have been derived from the chimpanzee haplotype by a G to C transversion at −1,882, consistent with either genetic drift or selection pressure for this haplotype in the human population. Five other minor haplotypes (4, 6, 8, 10, and 11) differ from haplotype 1 by other single nucleotide substitutions but retain the C allele at −1,882. As this otherwise conserved position lies adjacent to a SRE, changes at this location could potentially alter *SLC22A8* expression in response to steroid signaling.

Analysis of a considerably larger, ethnically diverse, set of human samples will be required to more fully understand less common and population-specific variations in *OAT* genes. Nevertheless, our data indicate that variation in the noncoding regions of these genes, particularly *SLC22A8*, may have an impact on human variation in handling of drugs and toxins by the basolateral OATs. Such regulatory polymorphisms are especially important given the low level of nonsynonymous polymorphisms so far observed in coding regions of these genes compared with other members of family such as *SLC22A11* and *SLC22A12* (Xu et al. 2005). Similar considerations apply to understanding the roles of SNPs in this subfamily on uric acid handling in gout, uric acid nephrolithiasis and human variations in serum uric acid, since OAT1, OAT3, and URAT1 are encoded by three genes proposed to regulate renal urate handling (reviewed in Hediger et al. 2005).

In mice, knockout data strongly suggest that most of the basolateral uptake of prototypical organic anions such as PAH, estrone sulfate and taurocholate, not to mention drugs like loop and thiazide diuretics, can be explained by the combined action of *SLC22A6* and *SLC22A8* (Sweet et al. 2002; Eraly et al. 2005). It is likely that this also applies to other common organic anion drugs, including NSAIDs, ACE inhibitors, methotrexate, certain antibiotics and certain antivirals (such as adefovir and cidofovir).

Interestingly, in mice with a *SLC22A8* functional deletion, *SLC22A6* function appears also to be reduced (Sweet et al. 2002). However, the impact of particular noncoding region polymorphisms on the transcription of *SLC22A6* and *SLC22A8* will need to be evaluated in an appropriate expression system, ideally one utilizing cloned human proximal tubule cultured cells known to express *SLC22A6* and *SLC22A8* message and protein. From the literature, it is not clear that such a system currently is available. Therefore, as a result of functional redundancy and the possible co-regulation of these closely linked or paired genes, polymorphisms on *SLC22A6* or *SLC22A8* 5′ regulatory and/or coding regions might affect organic anion transport to a much greater degree than polymorphisms in other gene pairs or families.

Together with the continuing analysis of coding region polymorphisms in *OATs* and other *SLC22* family members, the type of approach we describe should eventually provide a useful database of polymorphisms that are potentially of functional importance in either regulating the actual transport (or, conceivably, targeting) process or message/protein levels. This set of polymorphisms can then be analyzed in well-defined clinical populations to determine whether variations correlate with differences in drug handling, susceptibility to toxicity or metabolic abnormalities, as evident in *SLC22A12* coding region variants of which affect serum uric acid levels (Enomoto et al. 2002; Anzai et al. 2005).

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