Drug Metabolism and Pharmacokinetics 30 (2015) 457–460

Contents lists available at ScienceDirect

Drug Metabolism and Pharmacokinetics

journal homepage: http://www.journals.elsevier.com/drug-metabolism-and-pharmacokinetics

SNP communication B

Single nucleotide polymorphisms of the SLC22A2 gene within the Xhosa population of South Africa

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ARTICLE INFO

Article history:
Received 17 September 2015
Received in revised form
6 November 2015
Accepted 11 November 2015
Available online 23 November 2015

Keywords:
Polymorphism
Haplotype
Genetic variability
SLC22A2
African populations

ABSTRACT

Human organic cation transporter 2 (hOCT2) is thought to play a critical role in the uptake, pharmacological effects and/or adverse effects of many cationic clinical therapeutics and xenobiotics. Moreover, genetic variations in hOCT2 gene, *SLC22A2*, are increasingly being recognized as a possible mechanism that can explain individual variation in drug response. To screen for variations in this gene, *SLC22A2* was directly sequenced in 96 healthy Xhosa individuals. A total of 27 variations, including three novel ones, were identified in *SLC22A2*: eight in exons, 15 in introns, and four in the 5′-untranslated region. The minor allele frequencies (MAF) of genetic variants observed in the Xhosa population were compared both to other African and other world populations. Seventeen of the variants observed in the *SLC22A2* gene of the Xhosa population were specific to/or occurred at a higher frequency in African populations or populations with a recent connection to the African continent.

1. Introduction

The hOCT2 is primarily expressed in the kidney and located at the basolateral membrane of renal proximal tubules [1,2]. Because of this tissue distribution and membrane localization hOCT2 is thought to play a critical role in the uptake, pharmacological effects and/or adverse effects of many cationic clinical therapeutics and xenobiotics [3]. Examples of clinical drugs transported by hOCT2 include metformin (antidiabetic), lamivudine (antiretroviral), cisplatin (antineoplastic) and cimetidine (antihistamine) [4–7]. In addition, hOCT2 is also involved in the translocation of endogenous bioactive amines such as dopamine and norepinephrine, and in the elimination of toxic substances such as the neurotoxin 1-methyl-4-phenyl-pyridinium (MPP^+) [1,8–10].

hOCT2 is encoded by the *SLC22A2* gene which is located on chromosome 6q26, and consists of 11 exons spanning approximately 37 kb [1,7,11]. Clinical studies and *in vivo* animal experiments with knockout mice have demonstrated that variation in the expression level of *SLC22A2* can be responsible for individual variation in pharmacokinetics. Moreover, *SLC22A2* genetic polymorphisms have been implicated in the altered function of hOCT2 which may lead to a change in the disposition and response of substrate drugs.

To date several single nucleotide polymorphisms (SNPs) have been identified in the *SLC22A2* gene of ethnically diverse populations [12–15]. Functional characterization have revealed that several of these SNPs affect the transport function of hOCT2 *in vitro* [14]. Although *in vivo* evidence for the involvement of these SNPs in clinical phenotype is limited, recent studies have shown that homozygous carriers of the hOCT2 variant A270S (rs316019) have a lower renal clearance of metformin compared to those carrying the homozygous wild-type [16,17]. Furthermore, this reduced-function *SLC22A2* SNP, rs316019, was also associated with reduced nephrotoxicity from cisplatin in cancer patients [18]. However, these pharmacogenetic association studies have primarily been conducted in non-African populations, usually Western European and North American Caucasians, and have focused on genetic variants which are common to these populations [19]. The results of these studies are often extrapolated for use and interpretation in other populations. This is in spite of the fact that variant allele frequencies in pharmacogenetic genes can differ significantly between populations and even within populations [20,21]. In addition, population-specific variants exist in non-Caucasians which will probably be more relevant to treatment/study outcomes then those found in Caucasians.

The HapMap and 1000 Genomes projects currently include information on the Luhya and Maasai of Kenya, Yoruba and Esan of Nigeria, Gambian of The Gambia, and the Mende of Sierra Leone. However, the current opinion is that the population genetics of

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http://dx.doi.org/10.1016/j.dmpk.2015.11.002

these groups cannot represent the total genomic diversity of the remaining populations in West and East Africa, nor the populations residing in southern Africa [22,23]. Moreover, the role of this genetic diversity in disease pathogenesis and treatment is currently not fully understood. Thus, in order to fully understand and correlate this genomic diversity with pharmacogenetic phenotypes, the extent of variation in pharmacogenetically relevant genes such as *SLC22A2* in more African populations needs to be studied. Therefore, the aim of this study was to determine whether the *SLC22A2* gene of the Xhosa population harbours any novel SNPs, using direct sequencing of the 11 exons and flanking intronic regions of the gene in 96 healthy individuals, and secondly, to compare the minor allele frequencies obtained for the Xhosa to the 1000Genomes estimates for other African, American, European and Asian populations.

2. Materials and methods

2.1. Subjects

Genomic DNA samples in the form of buccal swabs were collected from healthy Xhosa subjects (n = 96). This study was approved by the Ethics Committee of the University of the Western Cape. Participants signed an informed consent for the collection, storage, and extraction of genomic DNA.

Table 1
Summary of SNPs identified with direct sequencing in the *SLC22A2* gene of Xhosa subjects.

dbSNP ID	Location	Nucleotide position Accession number (NC_000006.12)	Position[a]	Nucleotide change	Amino acid position	Flanking sequence (5′–3′)	Amino acid change	MAF	HWE
rs55920607	5′-UTR	160259003	−246	G>A		ACACCTCTTGGTCAATATTATTTGT**G**/**A**CTGTCCGTAGGACCCTCACTCGAGT		0.084	0.370
rs59695691	5′-UTR	160258952	−195	T>C		CCCGTAAACCCTTCACGTCTTCCTG**T**/**C**ACGTGGGGGCGACCTCCCCACGTGG		0.263	0.000
rs572296424	5′-UTR	160258913	−156	C>T		TTCAGGGCAGGGCCTTTCCTTGGTC**C**/**T**AGCTGACTTCAAAGGTGCACCCCTC		0.005	0.959
rs150063153	5′-UTR	160258852	−95	T>G		AACGTCTCCATTTGAGGGGAGAAAC**T**/**G**GAAGACCGGTCCCAAACACGACTCG		0.016	0.876
rs7727144	Exon 1	160258476	282	C>T	94	AGTCGAAGGTGCTCTGGTTCCAGTC**C**/**T**ACCTCGTAGCGCCTACACTGTCTTG	Val>Val	0.011	0.914
rs624249	Exon 1	160258368	390	C>A	130	CGGCCCTGCCGACCCACATGCTCTG**C**/**A**GGACCGAGCAGGTAGCAGTGGCTCC	Thr>Thr	0.128	0.566
rs112210325	Exon 1	160258359	399	C>A	133	CGACCCACATGCTCTGCGGACCGAG**C**/**A**AGGTAGCAGTGGCTCCATTCTCTCA	Ser>Ser	0.012	0.913
rs8177511	Intron 2-3	160250720	−18	A>G		GGCCAAACCTGCAGGAAGAAAAACA**A**/**G**AGAGAGGGAATTGAATTAATTTTGA		0.026	0.793
rs112710522	Intron 3-4	160250473	+75	T>C		TTTTATCTCAGTCCACCCCCCGCCG**T**/**C**ACGTTCTTTTCCCTGGGTCGAAGTT		0.086	0.581
rs372467753	Intron 4-5	160247329	−31	T>C		CCCTACCCCATTCCTCCTAAGTCAT**T**/**C**CTCAACGGGAGGCGAGTGGAACATG		0.011	0.958
rs316019	Exon 4	160249250	808	A>C	270	AGCAAGAAGAAGAAGTTGGGCAGAG**A**/**C**AACTGTGAACTGCAACCACCTCCAG	Ser>Ala	0.149	0.090
rs112425400	Intron 4-5	160247418	−120	C>T		CTTGGTGTATAGGGGGATGTGCTCA**C**/**T**AATAAAAGAAACCTCTAGGTTGACA		0.011	0.917
rs2279463 (CKD)	Intron 4-5	160247357	−59	A>G		CTGAATCCTCCTTACCCCATCCCCC**A**/**G**TTTTTTTATAATCAGATTTCTCTGA		0.183	0.536
MBPG_OCT2003	Intron 6-7	160245374	+65	C>A		GGATGAGGTCATGTTTTCTTCCCTT**C**/**A**CTTACTATGGATGACTGTGATTAAA		0.010	0.918
rs115889347	Intron 6-7	160245346	+93	C>T		TTGCTGCCCACCGTCAGCGCTAATA**C**/**T**CGGGATGAGGTCATGTTTTCTTCCC		0.005	0.959
rs617217	Intron 6-7	160245324	+115	C>G		CCGGTATTAGCGCTGACGGTGGGCA**C**/**G**CAATGTGGGTTGTGTCTGGTAGGTT		0.278	0.661
rs8177516	Exon 7	160243653	1198	G>A	400	GCCCAAGGGTAACGGCGTCCRATGC**G**/**A**GTCGATGGTGAGGATGATCATGAAG	Arg>Cys	0.052	0.590
rs8177517	Exon 8	160242388	1293	T>G	432	AAGGGAGAATCTAGATGTTACCGAT**T**/**G**TTTAATAATAGAGTACGAACCCTTC	Lys>Gln	0.011	0.917
rs17588242	Intron 8-9	160242198	+96	T>C		CGTCTGTTTCCTATAGAATGGAAGT**T**/**C**TTGTGTCACATTCCCTTCCACTCTT		0.011	0.917
rs11967308	Intron 9-10	160241327	+147	C>T		AATTACTAGGCACATCCAGGAAGAA**C**/**T**GCAAGCCACAGACACATCATTACTA		0.146	0.973
rs114897022	Intron 9-10	160241316	+158	T>C		ACAGACACCGAACGCAAGAAGGACC**T**/**C**ACACGGATCATTAATCATTATAATA		0.016	0.876
MBPG_OCT2005	Intron 9-10	160241261	+213	A>T		ATTAGTAATACTAATCAATAATACT**A**/**T**GTTCAGTATTCATAATATTATCATC		0.005	0.959
rs557733251	Intron 9-10	160241202	+272	T>C		ATGAGTTCATACCCTGAGGACGGTA**T**/**C**CTCCGTCTTACAACTTCTCTTCTTA		0.005	0.959
rs316003	Exon 10	160224800	1506	G>A	502	CCAGACCTCCAGCAACCAAGCCAAG**C**/**T**ACGCCTGAAAGCCAAACAGATGAAT	Val>Val	0.333	0.635
MBPG_OCT2007	Intron 10-11	160217752	−254	C>A		TCTCTATTACAGAGAAAGGTGAACA**C**/**A**CCTAAAAAAGGAACTTATTTAGGCC		0.005	0.959
rs3103352	Intron 10-11	160217693	−195	G>A		AAGTTGTTCTATTAAAATCCTTATT**G**/**A**AGACAGCTGTACTCAATAGTTGTTC		0.235	0.00015
rs139045661	Exon 11	160217445	1656	A>T	552	CGGTCTCTCTTCTTAGTTCAATGGA**A**/**T**TGTCTAGTTTCTGAACTTGGAGGTA	Ile/Asn	0.016	0.876

[a] From the translational initiation site or the nearest exon.