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CYP3A5 genetic polymorphisms in different ethnic populations

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Abbreviations:

A-RFLP: amplified-restriction fragment length polymorphism; PCR: polymerase chain reaction;

SNP: single nucleotide polymorphism

Abstract

Cyp3A5 activity varies between any given ethnic population suggesting that genetic variation within Cyp3A5 gene may be the most important contributor to interindividual and interracial differences in Cyp3A-dependent drug clearance and response. The full extent of Cyp3A5 polymorphism in a Caucasian and an indigenous African populations was analyzed using DNA direct sequencing procedures. The presence of 10 and 12 single nucleotide polymorphisms (SNPs) were detected in the Caucasian and African samples, respectively. Thirteen novel mutations occurring at low frequencies were identified in these populations. Significant differences were observed in the distribution of Cyp3A5*3, Cyp3A5*6, and Cyp3A5*7 alleles among Caucasian and African populations. The frequency of Cyp3A5*3 allele in Caucasian Canadians (~93%) is higher than in Zimbabweans (77.6%) ($p<0.001$). In contrast, Cyp3A5*6 and Cyp3A5*7 alleles are relatively frequent in Africans subjects (10-22%) but absent in Caucasians ($p<0.001$). These differences may reflect evolutionary pressures generated by environmental factors in geographically distinct regions. However, the genetic polymorphism of Cyp3A5 alone does not explain the inter-individual differences in Cyp3A mediated metabolism.

Cytochromes in the P450-3A family are estimated to participate in the metabolism of 40-60% of all clinically administered drugs. Specifically, they catalyze the oxidative, peroxidative, and reductive metabolism of many endogenous substrates and xenobiotics (Vazquez, 1997). The Cyp3A family is composed of four enzymes: Cyp3A4 the major isoform, Cyp3A43, Cyp3A5 and Cyp3A7. Cyp3A43 is expressed at very low levels in adult livers, accounting for only 0.1-0.2% of Cyp3A4 transcripts (Westlind et al., 2001). Cyp3A7 is primarily expressed in the fetal liver but can also be present in small amounts in some adult livers (Schuetz et al., 1994). The contribution of Cyp3A43 and Cyp3A7 to the metabolism of Cyp3A substrates in adults is therefore thought to be negligible. Cyp3A4 and Cyp3A5 are expressed primarily in adult human liver and the mucosa of the intestine and account for the majority of the catalytic activity of this enzyme subfamily (Wrighton et al., 1990; Kuehl et al., 2001). Substantial interindividual differences in Cyp3A enzyme expression contribute to variation in oral bioavailability and systemic clearance of Cyp3A substrates. The Cyp3A5 contribution to drug metabolism has been reported to vary from 6-99% of the total Cyp3A activity in different populations (Wrighton et al., 1990; Kuehl et al., 2001). Cyp3A5 is reported in detectable amounts in only 10-30% of adult Caucasians and Asians (Lee et al., 2003), while 60% of African Americans express the protein (Kuehl et al., 2001). These variations may be due, on one hand, to the modulation of Cyp3A expression through a wide array of environmental factors and drug-drug interactions or, on the other hand, to genetic variations.

Therefore, Cyp3A5 may be an important genetic contributor to interindividual and interracial differences in Cyp3A-dependent drug clearance and response. To date most studies on Cyp3A5 polymorphism have been conducted in populations from industrialized countries. The distribution of Cyp3A5 genetic variants in people living in developing countries may differ from that of people living in industrialized countries due to the selection pressure exerted on specific alleles by different environmental factors present in these geographic areas. The objective of our study was to analyze the full extent of Cyp3A5 polymorphism in Canadian Caucasians and indigenous African populations. To our knowledge, this is the first study to

systematically examine the nucleotide sequence diversity of Cyp3A5 gene in a large number of samples collected from indigenous Africans.

Material and Methods

Our samples consisted of stored DNA extracts from 100 unrelated Zimbabweans of the Shona ethnic group recruited in the ZVITAMBO project and 77 unrelated Caucasians from Quebec (Canada). The use of theses samples for the present study was approved by ethics committees. DNA was extracted from whole peripheral blood using standard phenol-chloroform extraction procedures. The nucleotide sequence variants in the promoter region and the 13 exons of Cyp3A5 gene were determined by direct sequencing method using 50 randomly selected samples of each population. The primers for PCR amplification of the promoter region and exon specific fragments were designed from the wild-type Cyp3A5 sequence (GenBank accession number AC005020). The primers were designed to cover the entire promoter region and each exon, as well as sequences at the exon-intron boundaries that are important for messenger RNA (mRNA) splicing. Details regarding primer sequences and annealing temperatures for amplifying Cyp3A5 DNA fragments for sequencing are shown in Table 1. Amplification reactions contained 200ng of DNA, 0.25mM of each dNTP (Pharmacia, Piscataway, NJ, USA), 1 X PCR buffer (Perkin-Elmer, Norwalk, CT, USA), 1.5mM $MgCl_2$ (Perkin-Elmer), 2.5 units of TAQ polymerase (Perkin-Elmer), and 15 pmole of primers in a total volume of 30µl. PCR cycling conditions included 5 minutes initial denaturation step at 95°C followed by 40 cycles of: 50 seconds at 95°C, 50 seconds at an appropriate annealing temperature, 50 seconds at 72 °C and a final extension step at 72°C for 5 minutes. The nucleotide sequences of the PCR products were determined by direct sequencing using BigDye terminator cycle sequencing reactions (Perkin Elmer). The reaction products were run in an automated DNA sequencing ABI PRISM 3100 capillary sequencer (Applied Biosystems, Foster City, CA, USA). All PCR products were sequenced in both directions.

Specific polymorphisms with the potential to modify enzymatic activity and protein structure were typed by amplified-restriction fragment length polymorphism (A-RFLP) in all the study samples. Cyp3A5*1B and Cyp3A5*1C alleles were determined by direct DNA sequencing. The primer sequences, annealing temperatures and restriction-endonuclease enzymes for the A-RFLP analyses are indicated in Table 2. Genomic DNA was amplified with the specific primers (Table 2) using the PCR conditions as described above. Amplified DNA products were then digested with the specific restriction enzymes according to the manufacturers' instructions (Table 2). The digestion products were subjected to 2.5% agarose gel electrophoresis and detected by staining with ethidium bromide. Allelic frequencies in our study populations were compared with published frequencies in other populations using Chi-squared test. Genotypic frequencies were compared with Hardy-Weinberg expectations using Chi-square analysis.

Results and Discussion

The DNA sequence analysis of the promoter and the entire coding regions of the Cyp3A5 gene revealed the presence of 10 and 12 SNPs in the Caucasian and Zimbabwean samples, respectively (Table 3). In the current study, all sequences were compared with the wild type Cyp3A5 sequence (GenBank accession number AC005020), and the positions reported are in reference to this sequence. Five novel variants including two located in the promoter region were identified in the Caucasian samples. The three novel nucleotide substitutions in coding regions are nonsynonymous mutations predicted to modify the amino acid composition of the protein; codons 309 (Thr→Asn), 323 (Thr→Asn), and 371 (Ile→Val). However, these mutations do not change the polarity of the protein; codons 309 and 323 (uncharged polar residue Thr to uncharged polar residue Asn) and codon 371 (non-polar residue Ile to non-polar residue Val). Eight new SNPs were detected in the African samples. Three are novel mutations in introns 3 (C→T), 8 (C→T) and 12 (T→C) and three others, at codons 218 (A→G), 295 (C→T), and 349 (C→T), are synonymous substitutions (silent mutations). The new nucleotide variants at codons 238 (T→C) and 460 (C→T) are nonconservative mutations resulting in a Val→Ala substitution and a stop codon leading to a

non-functional truncated protein, respectively. The codon 238 substitution (non-polar residue Val to non-polar residue Ala) does not change the polarity and only slightly modifies the structure (addition of a methyl group) of the protein. This mutation would therefore be unlikely to cause a modification in the protein due to a change in polarity or sterical hindrance. All the novel nonsynonymous mutations found in the Caucasian and African samples may have the potential to modify the amino acid composition of the protein but do not affect the polarity of the protein and occur at a very low frequency in these populations. Therefore, it seems improbable that they would play an important role in the Cyp3A5- related metabolic activities in these populations.

The distribution of Cyp3A5 alleles is shown in Table 4. The genotypic distribution of SNPs at each position is in Hardy-Weinberg equilibrium ($p > 0.5$) for both populations analysed in the present study. There are some significant differences in Cyp3A5 allelic distribution between indigenous Africans and Caucasians particularly for Cyp3A5*3, Cyp3A5*6, and Cyp3A5*7 alleles. The frequency of Cyp3A5*3 allele in Caucasian Canadians (~93%) is higher than in Zimbabweans (77.6%) ($p<0.001$). In contrast, Cyp3A5*6 and Cyp3A5*7 alleles are relatively frequent in Africans subjects (10-22%) but absent in Caucasians ($p<0.001$). The Cyp3A5*3 and Cyp3A5*6 alleles code both for splicing defects (Kuehl et al., 2001; Hustert et al., 2001) resulting in modified mRNA that may generate defective Cyp3A5 enzymes. The Cyp3A5*7 allele has a single base insertion at codon 346 that causes a frameshift resulting in a truncated, non-functional enzyme (Hustert et al., 2001). These findings raise the possibility that indigenous Africans may be greater metabolizers than Caucasians**,** since the Cyp3A5*3 allele is observed less frequently in the former group. However the presence of Cyp3A5*6 and Cyp3A5*7 in the indigenous African group may compensate for the relatively low frequency of the Cyp3A5*3 allele resulting in metabolic capabilities similar to those of Caucasians. Finally SNP 31611**,** which is located in the 3'UTR region of the Cyp3A5 gene**,** was detected in 60% of African samples and only in 8.6% of Caucasian samples ($p<0.001$). The possible effects of SNP 31611 on Cyp3A5 enzyme are currently not known.

It has been reported that up to 2-3 fold enhancement of Cyp3A5 activity can be achieved in any given ethnic population ((Schuetz et al., 1994). This observation has led to the suggestion that the genetic variation in Cyp3A5 expression is a major determinant of Cyp3A-dependent drug metabolism in human (Chou et al., 2001). Although some previous studies have attempted to correlate the metabolic capabilities of different patients with genotype, a clear relationship between the levels of Cyp3A5 expression and or activity and genetic markers remains to be established (Westlind et al., 2001; Wrighton et al., 1990; Kuehl et al., 2001; Jounaidi et al. 1996). It has also been reported that individuals homozygous for Cyp3A5*3 can express both wild type and variant (SV1) mRNA (Westlind et al., 2001). Interestingly, the most frequent polymorphisms in all ethnic populations, code for splicing defects (Cyp3A5*3 and Cyp3A5*6). This could suggest that these genetic factors predispose to downstream modulation of Cyp3A5 activity and expression and could therefore be the base of the interindividual variation which is observed for Cyp3A mediated metabolism. Ultimately it seems that the metabolic capacities of Cyp3A5 are intertwined into a complex procedure determined by both the genetic make-up of an individual as well as external factors, such as xenobiotics, influencing gene expression (Gibson et al.,2002).

In summary, we have conducted a thorough analysis of the nucleotide sequence of Cyp3A5 gene in samples collected from Canadian Caucasians and indigenous Zimbabweans. Several novel and nonconservative mutations, with respect to predicted amino acid composition and function of the protein, were identified albeit at low frequencies. The data from this study and others (Wrighton et al., 1990; Chou et al., 2001; Kuehl et al., 2001; Hustert et al., 2001; Lee et al., 2003) demonstrate that the allelic distribution of Cyp3A5 gene differs widely in populations from industrialized and developing countries, presumably due to geographically-determined selection pressures. However, the genetic polymorphism of Cyp3A5 can't explain the interindividual differences reported in Cyp3A mediated metabolism. Additional studies will have to be undertaken examining a large number of parameters including:

genotype, mRNA expression, drug-drug interaction as well as external influences in order to more fully understand the factors hat determine the metabolic capabilities of the Cyp3A5 family enzymes.

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Footnotes

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Table 1 Primer sequences annealing temperatures for amplify the promoter and coding regions of Cyp3A5 for sequencing.

Exon	Primer Name	Primer sequence	Annealing Temperature	Fragment size (bp)
Promoter[a]	Cyp3A5F	GAG GAT GGA TTT CAA TTA TTC TA	55 °C	387
	Cyp3A5R	GTC CAT CGC CAC TTT CCT TC		
Exon 2	5Ex2f	CTC ACC AGC CCT CTG ATC TAT AAA	64 °C	238
	5Ex2r	AAG GAG GGG CAT TTT TAC TGA TGG		
Exon 3	5Ex3f	CCC CAA TTA GAG GTA GGG TTT A	60 °C	175
	5Ex3r	GGT AAC CTC CTC ACA GTA GC		
Exon 4	5Ex4f	GGC TAG TGA AGT TTA ATC AGC T	56°C	190
	5Ex4r	ATT TAA TCA GTG GAT CAA TC		
Exon 5	5Ex5f	TTG TGC AAC CAT GAA GAT CA	60°C	238
	5Ex5r	CTT TCT ACC TGT CCC CAG AT		
Exon 6	5Ex6f	CCA TAT CCT TCT GGG ACT TGA GTC TG	64 °C	215
	5Ex6r	CAT GGC AGG CAG CTG GAA GGG		
Exon 7	5Ex7f	GCA TGT ATA GTG GAA GGA CG	60 °C	275
	5Ex7r	GAA TTA TAT GTC AAG AAA GCA G		
Exon 8	5Ex8f	GTA AAG TTT GCA TTT TCA AT	60 °C	256
	5Ex8r	CAT GCT CTA TCA TGT GTA TAA		
Exon 9	5Ex9f	GCC ATA GGG AGG TTG AGG GAG GGA A	64 °C	234
	5Ex9r	CCT CCC TCT TAG TGT CCC CGC CAG		
Exon 10	5Ex10f	CTA AGC TGT GAT GTT GTA CGT TG	64 °C	348
	5Ex10r	TCC TAC ATT ATG TCA GTG AAG GAA TC		
Exon 11	5Ex11f	CTT CAC GAA TAC TAT GAT CAT TTA CC	60 °C	422
	5Ex11r	GGC AGA ATA TGC TTG AAC CAG C		
Exon 12	5Ex12f	GGG TTG TTC TTA AGT AAG AAC CCC T	64 °C	374
	5Ex12r	GAT GGA TCC AAG TAG GTT CTT TGG CC		
Exon 13	5Ex13f	GAT ACA TGG TGT TAA GAG TCG T	60 °C	422
	5Ex13r	TCC TTT ATA CTA CAT AAT GCA CAA C		

[a] (Kuehl et al., 2001)

Table 2 Primer sequences, annealing temperatures and restriction-endonuclease enzymes for A-RFLP typing of Cyp3A5

Allele/SNP	Primer Name	Primer sequence	Annealing temperature	Restriction enzyme	Digestion products
Cyp3A5*2	5Ex11f	CTT CAC GAA TAC TAT GAT CAT TTA CC	60 ^{0}C	Tsp5091 (NEB)	Wt: 310,90,22 Mt:187,123,90,22
	5Ex11r	GGC AGA ATA TGC TTG AAC CAG C			
Cyp3A5*3	3A5A3f	CAT GAC TTA GTA GAC AGA TGA	56 ^{0}C	Ssp I (NEB)	Wt: 148,125,20 Mt: 168,125
	3A5A3r	GGT CCA AAC AGG GAA GAA ATA			
Cyp3A5*5	3A5A5f	CCA TGA AGA TCA CCA CAA CT	56 ^{0}C	Nla III (NEB)	Wt: 218 Mt: 172,46
	3A5A5r	CCT GTC CCC AGA TTC ATT C			
Cyp3A5*6	5Ex7f	GCA TGT ATA GTG GAA GGA CG	60 ^{0}C	Dde I (NEB)	Wt: 103,60,87,25 Mt: 128,87,60
	5Ex7r	GAA TTA TAT GTC AAG AAA GCA G			
SNP 31611 (3'UTR)	C3A512f	ACC CTA AGT GGAGGA ATG AGT TAT TCT AAG T	60 ^{0}C	Sca 1 (NEB)	Wt: 209 Mt: 181,29
	5Ex13r	TCC TTT ATA CTA CAT AAT GCA CAA C			

Abbreviations, A-RFLP: amplified-restriction fragment length polymorphism; NEB: New England Biolabs; SNP: single nucleotide polymorphism; Wt: wild-type; Mt: mutant

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Table 3 Cyp3A5 nucleotide sequence variations observed in Caucasian Canadians and Zimbabweans

Location		Allele	Nucleotide substitution	Genomic position	Observed in (frequency %)	Amino acid change	Reference citation
Promoter		Cyp3A5*1C	C/**T**	15 839	Cau. (4.6)		[1,2]
Promoter			G/**A**	15 588	Cau. (0.7)		New
Promoter			G/**A**	15 660	Cau. (0.5)		New
Intron 3		Cyp3A5*3	A/**G**	22 893	Afr. (77.6)	Splicing defect	[1,2]
					Cau. (92.9)		
Intron 3			C/**T**	23 114	Afr. (6.0)		New
Exon 7	Codon 208	Cyp3A5*6	G/**A**	30 597	Afr. (22.0)	Splicing defect	[1,2]
Exon 7	Codon 218		A/**G**	30 627	Afr. (2.0)	None (Pro)	New
Exon 8	Codon 238		T/**C**	31 756	Afr. (1.0)	Val →Ala	New
Intron 8			C/**T**	32 867	Afr. (1.0)		New
Exon 10	Codon 295		C/**T**	35 171	Afr. (1.0)	None (Leu)	New
Exon 10	Codon 309		C/**A**	35 210	Cau. (1.0)	Thr→Asn	New
Exon 10	Codon 323		C/**A**	35 252	Cau. (1.0)	Thr→Asn	New
Intron 10			A/**G**	42 957	Cau. (4.0)		[2]
Exon 11	Codon 346	Cyp3A5*7	Ins T	43 039	Afr. (10.0)	Frameshift	[2]
Exon 11	Codon 349		C/**T**	43 050	Afr. (1.0)	None (Ala)	New
Exon 11	Codon 371		A/**G**	43 114	Cau. (1.0)	Ile→Val	New
Exon 11	Codon 398	Cyp3A5*2	C/**A**	43 196	Cau. (0.7)	Thr→Asn	[2]
Exon 12	Codon 460		C/**T**	45 701	Afr. (1.0)	Gln→Stop	New
Intron 12			T/**C**	47 406	Afr. (3.0)		New
3'UTR		SNP 31611	T/**C**	47 518	Afr. (60.0)		[2]
					Cau. (8.6)		

Variant nucleotides are in bold. Genomic positions are based on GenBank sequence AC005020

[1] Kuehl et al., 2001; [2] Hustert et al., 2001

Abbreviations, Afr: African (Zimbabwean); Cau: Caucasian Canadian

Table 4. Cyp3A5 allelic frequencies (%) in different ethnic populations.

Allele	Caucasian Canadian (*n*=154)	Zimbabwean (*n*=200)	Caucasian European	African-American	Asian	References
Cyp3A5*1B	0.0	0.0	0.5-3.0	0.0	n.d	[1,2]
Cyp3A5*1C	4.6	0.0	3.0	7.0	0.0	[1-3]
Cyp3A5*2	0.7	0.0	2.0	0.0	n.d	[2]
Cyp3A5*3	92.9	77.6	70.0	27.0-50.0	75	[1-3]
Cyp3A5*5	0.0	0.0	n.d	n.d	0.9	[4]
Cyp3A5*6	0.0	22.0	0.0	13.0	0.0	[3]
Cyp3A5*7	0.0	10.0	0.0	10.0	0.0	[2,3]

Abbreviations, Afr. Am.: African Americans; Cau: Caucasians; *n*= number of alleles; n.d: not determined

[1] Cau. *n*= 118; Afr. Am. *n*= 30 (Kuehl et al., 2001); [2] Cau. *n*= 160; Afr. Am. *n*= 90 (Hustert et al., 2001); [3] Asians *n*= 48; Afri. Am. *n*= 15; Cau. *n*= 48 (Lee et al., 2003); [4] Asians *n*=220 (Chou et al., 2001).