Short Communication

Prevalence of Polymorphisms in the Human UDP-Glucuronosyltransferase 2B Family: *UGT2B4(D^{458}E)*, *UGT2B7(H^{268}Y)*, and *UGT2B15(D^{85}Y)*[1]

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Abstract

UDP-glucuronosyltransferases (UGTs) of the UGT2B family conjugate steroid hormones as well as bile acids and xenobiotics. UGT2Bs are expressed in numerous human tissues, such as skin, breast, prostate, adipose, and intestine and are hypothesized to modulate steroid metabolism and excretion. Polymorphisms have been identified that may modify substrate specificities or enzyme activities of UGT2B family isozymes. We determined the prevalence of the *UGT2B4(D^{458}E)*, *UGT2B7(H^{268}Y)*, and *UGT2B15(D^{85}Y)* polymorphisms in a sample of 233 individuals. The allele frequencies were significantly different ($P < 0.02$) between individuals of Caucasian and Asian descent for all three polymorphisms. In Asians ($n = 32$), the frequencies of the *UGT2B4(D^{458})*, *UGT2B7(H^{268})*, and *UGT2B15(D^{85})* alleles were 1.00, 0.73, and 0.64, respectively, whereas, in Caucasians ($n = 202$), the frequencies of *UGT2B4(D^{458})*, *UGT2B7(H^{268})*, and *UGT2B15(D^{85})* were 0.75, 0.46, and 0.45, respectively. The distribution of the *UGT2B4(D^{458}E)*, *UGT2B7(H^{268}Y)*, and *UGT2B15(D^{85}Y)* genotypes also differed by ethnic group ($P < 0.0001$, $P = 0.002$, and $P = 0.02$, respectively). All Asians were homozygous for *UGT2B4(D^{458})* and had a greater than 2-fold higher prevalence of the *UGT2B7(H^{268})* and *UGT2B15(D^{85})* homozygous genotypes compared with Caucasians: 56.2% *versus* 21.8%, and 46.9% *versus* 22.3%, respectively. Concomitantly, only 9.4% of Asians were *UGT2B7(Y^{268})* homozygous and 18.7% were *UGT2B15(Y^{85})* homozygous compared with 29.2% and 32.2%, respectively, of Caucasians. The data suggest that there may be large differences in *UGT2B* polymorphisms between Asians and Caucasians. This warrants evaluation both in larger, multiethnic cohorts and in relation to known ecological differences in risk of sex hormone-dependent cancers.

Introduction

In humans, two families of UGTs[3] catalyze the transfer of the glucuronyl group from uridine 5′-disphosphoglucuronic acid to endogenous molecules, such as bile acids, steroids, and thyroid hormones, and a wide range of exogenous substrates. Generally, the UGT1 family catalyzes the glucuronidation of bilirubin and xenobiotic phenols as well as some steroids (1). The UGT2 family includes the subfamilies 2A and 2B; the 2B enzymes glucuronidate primarily steroids (2). UGTs play an important role in detoxification and chemoprotection (3), as well as drug metabolism and regulation of steroid hormone levels (2, 4). Polymorphisms in the UGTs are postulated to contribute to interindividual variation in drug disposition (5) and certain *UGT1A* variants are known to be associated with altered bilirubin excretion (6). It is highly likely that certain UGT polymorphisms may also influence steroid hormone metabolism and cancer susceptibility; however, the relationship between genetic variation in glucuronidation and cancer risk has yet to be explored.

Polymorphisms have been identified in at least three of the human *UGT2B* genes: *UGT2B4*, *UGT2B7*, and *UGT2B15* (7–9). Reported nucleotide sequence differences in *UGT2B4* lead to amino acid changes at positions 109, 396, and 458. The variant UGT2B4(L^{109,396}D^{458}), isolated from human liver, has leucine (L), instead of phenylalanine (F) residues at amino acids 109 and 396 (7, 10). A difference of two nucleotides also leads to another single amino acid change of aspartate (D) to glutamate (E) at position 458 (7). UGT2B4 is primarily involved in the conjugation of catechol estrogens, bile acids (specifically hyodeoxycholic acid), and certain exogenous phytochemicals (7). Both UGT2B4(D^{458}) and (E^{458}) are expressed in liver and a wide range of extrahepatic tissues, including those that are targets for steroid hormones; however, there is no apparent difference in substrate specificity between the two forms (7). Lévesque *et al.* (7) reported that in a sample of 26 Caucasian individuals, the frequency of the variant *E^{458}* allele was 0.385. The authors did not detect the presence of the *UGT2B4(L^{109,396}D^{458})* variant in any of the tissues or genomic DNA sampled; however, they suggested that this may be a rare allele not found in their sample population.

In UGT2B7, there is an amino acid change from histidine (H) to tyrosine (Y) at amino acid 268 (8), the proposed location of the substrate-binding site (11). The prevalence of the two alleles and a corresponding phenotypic difference have not been determined. UGT2B7 glucuronidates 4-hydroxycatechol estrogens (12) and mono- and dihydroxylated androgens with a hydroxyl group in the 3α, 6α, and 17β positions; however, UGT2B7 has the highest activity toward steroids containing a 3α-hydroxy moiety (13, 14). UGT2B7 expression has been

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[3] The abbreviation used is: UGT, UDP-glucuronosyltransferase.

detected in liver, kidney, pancreas, brain, and the gastrointestinal tract (15–17).

In *UGT2B15*, a thymine in place of a guanine leads to an amino acid change at position 85 from aspartic acid (D) to tyrosine (Y; Ref. 9). UGT2B15 is expressed in numerous human tissues (*e.g.*, liver, kidney, testis, mammary gland, prostate, and lung; Ref. 9). This isozyme catalyzes the glucuronidation of a wide range of substrates, including simple phenolic compounds, drugs, and C_{19} steroids, such as 5α-androstane-3α,17β-diol and dihydrotestosterone, at the 17β position (18, 19). Coumarins, flavonoids, and anthraquinones, phytochemicals that are present in high amounts in certain plant foods, also are glucuronidated by UGT2B15 (18). To date, only one study has examined the prevalence of the *UGT2B15* polymorphic allele; Lévesque *et al.* (9) determined that of a sample of 27 Caucasians, 6 (19%) were homozygous for Y^{85} (Y^{85}/Y^{85}), 5 (22%) were homozygous for D^{85} (D^{85}/D^{85}), and 16 (73%) had both alleles (D^{85}/Y^{85}).

The purpose of our work was to determine the prevalence of the described genetic polymorphisms in *UGT2B4*, *UGT2B7*, and *UGT2B15* in a sample of individuals from the Seattle, Washington area.

Materials and Methods

Two hundred and forty-five nonsmokers, 20–40 years of age, from the Seattle area were screened for participation in a cross-sectional study of diet and biotransformation enzymes. Exclusion criteria included history of gastrointestinal disorders, weight loss or gain >4.5 kg within the past year, major changes in eating habits within the past year (*e.g.*, adoption of a different dietary pattern), exercise regimens requiring significant short-term dietary changes, antibiotic use within the past 3 months, body weight >150% of ideal, current drug therapy for a diagnosed disease, chronic nonsteroidal anti-inflammatory drug use, alcohol intake greater than two drinks per day (two drinks being equivalent to 720 ml of beer, 240 ml of wine, or 90 ml of hard liquor), occupational exposure to smoke or organic solvents, chronic passive exposure to tobacco smoke, intake of pharmacological doses of dietary supplements, and serum alanine aminotransferase concentrations above the normal range.

All participants had venous blood samples drawn for genomic DNA collection. DNA was extracted from lymphocytes according to standard methods using a proteinase K digestion followed by phenol-chloroform extractions (20). A demographic and health questionnaire was completed. Information requested on the questionnaire included usual diet (*e.g.*, vegetarian, diabetic, low-fat), food preferences, alcohol intake, medical history, vitamin/mineral and herbal supplement information, usual activity, medications, environmental exposures, and ethnic/racial background. The study design was approved by the Institutional Review Board: Human Subjects Committee at the Fred Hutchinson Cancer Research Center. Informed written consent was obtained from all participants prior to the start of the study.

Determination of UGT2B4, UGT2B7, and UGT2B15 Genotypes

The *UGT2B4* $F^{109}L$, $F^{396}L$, and $D^{458}E$; *UGT2B7*; and *UGT2B15* genotypes were determined using an oligonucleotide ligation assay (21, 22). Amplification of the correct PCR fragments was confirmed by sequencing.

UGT2B4. To distinguish the *UGT2B4*($D^{458}E$) (GenBank accession nos. AJ005162 and AF064200, respectively) and *UGT2B4*($L^{109,396}$,D^{458}) (GenBank accession no. AF081793) alleles, the polymorphisms at amino acids 109, 396, and 458 were determined. Three fragments were amplified by PCR using the following primers: for $F^{109}L$, FP1 (5′-GAGGATATTATCAAGCAGCT-3′) and RP1 (5′-CAGCATCTGCAAGAACAACA-3′); for $F^{396}L$, FP2 (5′-ACCTCATGGTGGAGCCAATG-3′) and RP2 (5′-ACATTGTGTGGAAGTCCAAA-3′); and for $D^{458}E$, FP3 (5′-TTCATCATGATCAACCAGTGA-3′) and RP3 (5′-CTTCCAGCCTCAGACGTAAT-3′). The PCR reactions contained 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 0.001% gelatin, 50 ng/μl BSA, 200 μM deoxynucleotide triphosphates (100 μM for $F^{109}L$ and $D^{458}E$), 150 nM amplification primers, 100 ng of genomic DNA, and 0.5 units of AmpliTaq DNA polymerase (Perkin-Elmer, Foster City, CA). The cycling conditions on a PTC-100 thermal cycler (MJ Research, Inc., Watertown, MA) were as follows: (*a*) for $F^{109}L$ and $F^{396}L$, 94°C for 5 min, followed by 30 cycles of 94°C for 30 s, 58°C for 45 s, and 72°C for 60 s and 1 cycle of 72°C for 5 min; and (*b*) for $D^{458}E$, 94°C for 5 min, followed by 30 cycles of 94°C for 30 s, 60°C for 45 s, and 72°C for 60 s and 1 cycle of 72°C for 5 min.

The $F^{109}L$, $F^{396}L$, and $D^{458}E$ polymorphisms were determined by oligonucleotide ligation assay using the primers listed in Table 1. The modification for the allele-specific primers was 5′-biotin and 5′-phosphate and 3′-digoxigenin for the common primer. For the ligation, the PCR reactions were diluted with 35 μl of 0.1% Triton X-100. The ligation reactions consisted of 10 μl of diluted PCR product, and 10 μl of 40 mM Tris-HCl (pH 8.0), 20 mM $MgCl_2$, 25 mM KCl, 2 mM DTT, 2 mM NAD^+, 0.1% Triton X-100, 16 fmol/μl biotinylated primer, 16 fmol/μl common primer, and 0.015 units of thermostable ligase (Epicentre Technologies, Madison, WI). The cycling conditions for the ligation were as follows: 15 cycles of 93°C for 30 s and 58°C for 2 min. The reaction was stopped with 10 μl of a buffer containing 0.1 M EDTA (pH 8.0) and 0.1% Triton X-100. The ligation reactions were then transferred into streptavidin-coated 96-well plates. After incubation at room temperature for 60 min, the plates were washed twice with 10 mM NaOH containing 0.05% Tween 20, followed by two washes with 200 μl of 100 mM Tris-HCl (pH 7.5), 150 mM NaCl, and 0.05% Tween 20. The plates were then incubated with 40 μl of a 1000-fold dilution of antidigoxigenin Fab fragment-phosphatase conjugate (0.75 units/μl; Boehringer Mannheim, Indianapolis, IN) for 30 min at room temperature. After four washes with 100 mM Tris-HCl (pH 7.5), 150 mM NaCl, and 0.05% Tween 20, the Life Technologies amplification system was applied for the color reaction according to the manufacturer's recommendations. The absorbance at 490 nm was recorded using a SpectraMax 250 plate reader (Molecular Devices, Sunnyvale, CA).

***UGT2B7*($H^{268}Y$)**. The *UGT2B7*($H^{268}Y$) polymorphism consists of a C-to-T point mutation, resulting in an amino acid change from histidine (H) to tyrosine (Y) at amino acid 268 (8). Primers 5′-AAGCTGACGTATGGCTTATT-3′ and 5′-CAAAATCAACATTTGGTAAGAG-3′ were used to amplify a 74-bp fragment of the *UGT2B7* gene containing the mutation. The PCR reactions contained 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 0.001% gelatin, 50 ng/μl BSA, 200 μM deoxynucleotide triphosphates, 200 nM amplification primers, 100 ng of genomic DNA, and 0.5 units of AmpliTaq DNA polymerase (Perkin-Elmer). The cycling conditions on a PTC-100 thermal cycler (MJ Research) were as follows: 94°C for 5 min, followed by 35 cycles of 94°C for 30 s, 61°C for 45 s, 72°C for 45 s and 1 cycle of 72°C for 5 min.

The primers for the ligation reactions were as follows: H^{268} (5′-CCTGGAATTTTCAGTTTCCTC-3′); Y^{268} (5′-CCT-

Table 1 *UGT2B4* genotyping strategy

	Sequence[a]
$F^{109}L$	
AJ005162	… GAACTTCCAAAAGACACATTTTGGTCATAT**T**TTTCACAAGTACAAGAAATCATGT …
AF064200	… GAACTTCCAAAAGACACATTTTGGTCATAT**T**TTTCACAAGTACAAGAAATCATGT …
AF081793	… GAACTTCCAAAAGACACATTTTGGTCATAT**C**TTTCACAAGTACAAGAAATCATGT …
Allele-specific primers	
109F	AAGACACATTTTGGTCATAT**T**
109L	AAGACACATTTTGGTCATAT**C**
Common primer	TTTCACAAGTACAAGAAATCA
$F^{396}L$	
AJ005162	… AATCCCTATGGTGGGCGTTCCATTG**T**TTGCAGATCAACCTGATAACATT …
AF064200	… AATCCCTATGGTGGGCGTTCCATTG**T**TTGCAGATCAACCTGATAACATT …
AF081793	… AATCCCTATGGTGGGCGTTCCATTG**C**TTGCAGATCAACCTGATAACATT …
Allele-specific primers	
396F	ATGGTGGGCGTTCCATTG**T**
396L	ATGGTGGGCGTTCCATTG**C**
Common primer	TTGCAGATCAACCTGATAAC
$D^{458}E$	
AJ005162	… CAACCAGTGAAGCCCCTTGA**TC**GAGCAGTCTTCTGGATTGAATTTGTCAT …
AF064200	… CAACCAGTGAAGCCCCTTGA**AA**GAGCAGTCTTCTGGATTGAATTTGTCAT …
AF081793	… CAACCAGTGAAGCCCCTTGA**TC**GAGCAGTCTTCTGGATTGAATTTGTCAT …
Allele-specific primers	
458D	CCAGTGAAGCCCCTTGA**TC**
458E	CCAGTGAAGCCCCTTGA**AA**
Common primer	GAGCAGTCTTCTGGATTGAA

[a] Boldface letters indicate nucleotide differences among sequences.

GGAATTTTCAGTTTCCAT-3′); and common primer (5′-ATCCACTCTTACCAAATGTTG-3′). The modifications for the primers were 5′-biotin for H^{268}- and Y^{268}-specific primers and 5′-phosphate and 3′-digoxigenin for the common primer. The ligation reactions were as described for *UGT2B4*.

UGT2B15(D*^{85}*Y). The *UGT2B15(D*^{85}*Y)* polymorphism consists of a G-to-T point mutation, resulting in an amino acid change from aspartic acid (D) to tyrosine (Y) at amino acid 85 (9). Primers 5′-GTTACTTTAGCTCTGGAAGC-3′ and 5′-AGAGCTTGTTACTGTAGTCAT-3′ were used to amplify a 333-bp fragment of the *UGT2B15* gene containing the mutation. The PCR reactions contained 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 0.001% gelatin, 50 ng/μl BSA, 100 μM deoxynucleotide triphosphates, 100 nM amplification primers, 100 ng of genomic DNA, and 0.5 units of AmpliTaq DNA polymerase (Perkin-Elmer). The cycling conditions on a PTC-100 thermal cycler (MJ Research) were as follows: 94°C for 5 min, followed by 35 cycles of 94°C for 30 s, 60°C for 45 s, 72°C for 60 s and 1 cycle of 72°C for 5 min.

The ligation was performed as described above for *UGT2B7*. The ligation primers for *UGT2B15* were D^{85} (5′-TCCTACATCTTTAACTAAAAATG-3′); Y^{85} (5′-TCCTACATCTTTAACTAAAAATT-3′); and common primer (5′-ATTTGGAAGATTCTCTTCTGAA-3′). The modifications for the primers were 5′-biotin for D^{85}- and Y^{85}-specific primers and 5′-phosphate and 3′-digoxigenin for the common primer.

Statistical Analysis

Statistical analyses were conducted using SAS software (Version 6.12 for Windows; SAS Institute Inc., Cary, NC). We measured differences between observed and expected *UGT2B4(D*^{458}*E)*, *UGT2B7(H*^{268}*Y)*, and *UGT2B15(D*^{85}*Y)* genotype frequencies using the χ^2 test and compared genotype frequencies between individuals of Asian and Caucasian background using Fisher's exact test.

Table 2 *UGT2B4(D*^{458}*E)*, *UGT2B7(H*^{268}*Y)*, and *UGT2B15(D*^{85}*Y)* allele and genotype frequencies in Asians and Caucasians

UGT2B polymorphisms	Asians (n = 32)	Caucasians (n = 202)
UGT2B4(D^{458}*E)*		
D^{458} allele frequency (number)	1.000 (64)	0.747 (302)
E^{458} allele frequency (number)	0	0.253 (102)
D^{458}/D^{458} genotype frequency	1.000	0.579
D^{458}/E^{458} genotype frequency	0	0.337
E^{458}/E^{458} genotype frequency	0	0.084
UGT2B7(H^{268}*Y)*		
H^{268} allele frequency (number)	0.734 (47)	0.463 (187)
Y^{268} allele frequency (number)	0.266 (17)	0.537 (217)
H^{268}/H^{268} genotype frequency	0.562	0.218
H^{268}/Y^{268} genotype frequency	0.344	0.490
Y^{268}/Y^{268} genotype frequency	0.094	0.292
UGT2B15(D^{85}*Y)*		
D^{85} allele frequency (number)	0.641 (41)	0.450 (182)
Y^{85} allele frequency (number)	0.359 (23)	0.550 (222)
D^{85}/D^{85} genotype frequency	0.469	0.223
D^{85}/Y^{85} genotype frequency	0.344	0.455
Y^{85}/Y^{85} genotype frequency	0.187	0.322

Results

The 245 individuals (146 women and 99 men) who were genotyped for this project described their ethnic backgrounds as follows: 202 Caucasian, 32 Asian (including individuals of Indian origin), 4 Hispanic, 2 Pacific Islander, 2 African, 1 Alaskan Native, 1 Asian/Caucasian, and 1 Native American/Caucasian. Data are presented only for Caucasians and Asians because the small numbers of individuals in the other categories preclude statistical comparison among these ethnic groups.

The *UGT2B4(D*^{458}*E)*, *UGT2B7(H*^{268}*Y)*, and *UGT2B15(D*^{85}*Y)* allele and genotype frequencies are presented in Table 2. We did

not detect the presence of the *UGT2B4(L*^{109,396}*,D*^{458}*)* allelic variant in any of the samples. The allele frequencies were significantly different ($P < 0.02$) between individuals of Caucasian and Asian descent for all three polymorphisms. Genotype frequencies for the *UGT2B4(D*^{458}*E)*, *UGT2B7(H*^{268}*Y)*, and *UGT2B15(D*^{85}*Y)* polymorphisms also differed significantly by ethnic group ($P < 0.0001$, $P = 0.0002$, and $P = 0.02$, respectively). All of the Asians were homozygous wild type (*D*^{458}/*D*^{458}) for *UGT2B4*. For *UGT2B7*, almost 60% of individuals of Asian background were *H*^{268}/*H*^{268} and only 9% were *Y*^{268}/*Y*^{268}, whereas among the Caucasians only 22% were *H*^{268}/*H*^{268} and 29% were Y^{268}/Y^{268}. Similarly, for *UGT2B15*, 47% of Asians were *D*^{85}/*D*^{85} and 19% were *Y*^{85}/*Y*^{85}, whereas 22% of Caucasians were *D*^{85}/*D*^{85} and 32% were *Y*^{85}/*Y*^{85}. Within the Asian and Caucasian samples, the genotype frequencies were in Hardy-Weinberg equilibrium.

Discussion

We have demonstrated that *UGT2B4(D*^{458}*E)*, *UGT2B7(H*^{268}*Y)*, and *UGT2B15(D*^{85}*Y)* are prevalent polymorphisms and that the genotype distributions appear to vary by ethnic group. All of the individuals of Asian descent in our study, compared with only 57.9% of Caucasians, were homozygous wild type for *UGT2B4(D*^{458}*)*. Although our sample of Asians is small, we would have expected to find the variant allele in ~13 individuals if the prevalence rate was similar to that in Caucasians. The variant *UGT2B7Y*^{268} and *UGT2B15Y*^{85} alleles also were significantly more common among Caucasians compared with Asians. The prevalence of the *UGT2B7 Y*^{268}/*Y*^{268} genotype was 3-fold higher in Caucasians than Asians. Similarly, the prevalence of the *UGT2B15 Y*^{85}/*Y*^{85} genotype was 1.7-fold higher in Caucasians than in Asians and also may be higher in our sample of Caucasians (32%) than in the sample of 27 Caucasians genotyped by Lévesque *et al.* (9), of which 19% were homozygous *Y*^{85}/*Y*^{85}.

The *UGT2B4(L*^{109,396}*,D*^{458}*)* variant allele appears to be very rare. Lévesque *et al.* (7) did not find expression of the *UGT2B4(L*^{109,396}*,D*^{458}*)* transcript in any tissue samples tested, nor did they find the allele in 26 samples of genomic DNA. Similarly, in our 10-fold larger sample, we also did not find any individuals with this allele.

The extent to which the 2B polymorphisms may influence xenobiotic and endogenous steroid conjugation remains to be determined. In UGT2B4, substitution of E for D at 458 probably is a relatively minor amino acid modification, and stably expressed UGT2B4(D^{458}) and UGT2B4(E^{458}) in HK293 cells show similar substrate specificity (7). In the case of *UGT2B7(H*^{268}*Y)*, H-to-Y constitutes a nonconservative amino acid change in the region of the substrate binding site. Consequently, Jin *et al.* (8) postulated that the polymorphism would probably affect substrate specificity. In addition, they reported that UGT2B7(Y^{268}), but not (H^{268}), conjugated menthol and androsterone. More recently, Cheng *et al.* (12) and Coffman *et al.* (23) reported that in the case of catechol estrogens, androsterone, opioids, and several xenobiotics, substrate glucuronidation efficiency did not differ between cells designed to express UGT2B7(H^{268}) or (Y^{268}).

The polymorphism in *UGT2B15(D*^{85}*Y)* does not appear to alter specificities among the substrates tested to date, but it does increase the V_{max} by 2-fold and may contribute to individual variability in glucuronidation observed with some drugs and other compounds (24). Specifically, UGT2B15(Y^{85}) has a higher V_{max} than UGTB15(D^{85}) for 5α-androstane-3α,17β-diol and dihydrotestosterone (9). Given the high prevalence of the variant allele (*Y*^{85}; 50%) and the small differences in kinetics, Lévesque *et al.* (9) suggested that differences in steroid hormone metabolism are unlikely to be observed *in vivo*, but that this polymorphism may contribute to individual variability in xenobiotic glucuronidation. On that basis, the implications of carrying the *Y*^{85} homozygous genotype are unclear; however, if the V_{max} is higher for the numerous phytochemicals that are metabolized by UGT2B15, one might postulate that these compounds would be cleared more rapidly and their potential chemopreventive effects would be reduced.

In conclusion, we have detected a high prevalence of the polymorphisms in *UGT2B4(D*^{458}*E)*, *UGT2B7(H*^{268}*Y)*, and *UGT2B15(D*^{85}*Y)* in a small, convenient sample of healthy individuals. In addition, we observed significant ethnic differences between Asians and Caucasians in the distribution of these polymorphisms. The relationship between *UGT2B* polymorphisms and cancer risk has not been explored; however, the role of UGT2Bs in the conjugation and excretion of steroid hormones and the international differences in risk of hormone-dependent cancers suggest that these enzymes may be important candidates for additional study. Whether the genotypic differences explain, in part, observed ethnic differences in steroid hormone profiles and drug metabolism remains to be determined. Our results suggest that further investigation of these polymorphisms in large, multiethnic cohorts is warranted.

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