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BRIEF REPORT

The Uridine Diphosphate Glucuronosyltransferase 2B15 D^{85}Y and 2B17 Deletion Polymorphisms Predict the Glucuronidation Pattern of Androgens and Fat Mass in Men

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Context: Previous *in vitro* studies have demonstrated that the UDP glucuronosyltransferase (UGT)2B15 and UGT2B17 glucuronidate androgens and their metabolites.

Objective: Our objective was to determine *in vivo* whether the UGT2B15 D^{85}Y and the UGT2B17 deletion polymorphisms predict androgen glucuronidation and body composition.

Participants: Two population-based cohorts including young adult (n = 1068; age = 18.9 yr) and elderly (n = 1001; age = 75.3 yr) men were included in the study.

Main Outcome Measures: Serum and urine levels of testosterone (T) and dihydrotestosterone (DHT) were measured by gas chromatography-mass spectrometry, and serum levels of the major glucuronidated androgen metabolites androstane-3α,17β-diol(androstanediol)-3-glucuronide, androstanediol-17-glucuronide, and androsterone-glucuronide were measured by liquid chromatography-tandem mass spectrometry. Body composition was measured by dual-energy x-ray absorptiometry.

Results: Both the UGT2B15 D^{85}Y and the UGT2B17 deletion polymorphisms were associated with serum levels of androstanediol-17-glucuronide ($P < 0.001$) but not with levels of androstanediol-3-glucuronide or androsterone-glucuronide in both cohorts. Glucuronidation of T and DHT was associated with the UGT2B17 deletion but not with the UGT2B15 D^{85}Y polymorphism, suggested by strong associations between the deletion polymorphism and urine levels of these two hormones. Both polymorphisms were associated with several different measures of fat mass ($P < 0.01$). The UGT2B17 deletion polymorphism was associated with insulin sensitivity ($P < 0.05$) as indicated by the homeostasis model assessment index.

Conclusions: The UGT2B15 D^{85}Y and the UGT2B17 deletion polymorphisms are both predictors of the glucuronidation pattern of androgens/androgen metabolites. Our findings indicate that UGT2B17 is involved in 17-glucuronidation of mainly T but also of DHT and androstanediol and that UGT2B15 is involved in the 17-glucuronidation of androstanediol. Furthermore, these two polymorphisms are predictors of fat mass in men. **(*J Clin Endocrinol Metab* 92: 4878–4882, 2007)**

CONJUGATION OF ANDROGENS with glucuronic acid has been suggested to play a role in the regulation of the intracellular levels of unconjugated androgens as well as their biological activities in tissues (1, 2). Circulating levels of androstane-3α,17β-diol(androstanediol)-glucuronides and androsterone-glucuronide, the two major 5α-reduced androgen metabolites in serum in men, originate from both the testicular androgen testosterone (T) and the adrenal C_{19} steroids (3). Androstanediol can be glucuronidated either at the 3α-hydroxy position (androstanediol-3-glucuronide) or at the 17β-hydroxy position (androstanediol-17-glucuronide). UDP glucuronosyltransferase (UGT)2B15 and UGT2B17 are two important enzymes for the glucuronidation of androgens and their metabolites (2). There is a G to T polymorphism in the *UGT2B15* gene, resulting in an aspartate (D^{85}) to tyrosine

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Abbreviations: CV, Coefficient of variation; Del, deletion; DHT, dihydrotestosterone; DXA, dual-energy x-ray absorptiometry; HOMA, homeostasis model assessment; T, testosterone; UGT, UDP glucuronosyltransferase; WT, wild type.

(Y^{85}) amino acid change at position 85 (4). A 150-kb deletion polymorphism spanning the whole *UGT2B17* gene has been identified (5, 6).

The aim of the present study was to determine *in vivo* whether the $D^{85}Y$ polymorphism of the *UGT2B15* gene and/or the deletion polymorphism of the *UGT2B17* gene predict the glucuronidation pattern of androgens/androgen metabolites and body composition in men.

Subjects and Methods

Study subjects

Young adult men from the population-based Gothenburg Osteoporosis and Obesity Determinants (GOOD) study (n = 1068, 18.9 ± 0.5 yr of age) (7) and elderly men from the Gothenburg part of the population-based MrOS Sweden cohort (n = 1001, 75.3 ± 3.2 yr of age) (8) were included. Information about prevalent diabetes mellitus (n = 110) was obtained through questionnaires in the elderly cohort. Informed consent was obtained from all study participants.

Dual-energy x-ray absorptiometry (DXA)

Body composition was assessed using Lunar Prodigy DXA for the young adult men (GE Lunar Corp., Madison, WI) or Hologic QDR 4500/A-Delphi for the elderly men (Hologic, Waltham, MA).

Assessment of sex hormones in serum

Serum levels were measured by validated high-sensitive gas chromatography-mass spectrometry [T limit of detection of 0.05 ng/ml and interassay coefficient of variation (CV) of 3.4% dihydrotestosterone (DHT) limit of detection of 0.02 ng/ml and interassay CV of 4.1%] and liquid chromatography-tandem mass spectrometry (androsterone-glucuronide limit of detection of 2.00 ng/ml and interassay CV of 3.7%, androstanediol-3-glucuronide limit of detection of 0.50 ng/ml and interassay CV of 10.7%, androstanediol-17-glucuronide limit of detection of 0.50 ng/ml and interassay CV of 5.3%) as previously described (9, 10). The serum samples in the MrOS cohort were fasting samples obtained before 0900 h. Serum samples in the GOOD study were nonfasting samples obtained over the whole day.

Assessment of sex hormones in urine

Urinary unconjugated steroids (typically < 1% of glucuronide fraction) including T and DHT plus their glucuronides were determined by gas chromatography-mass spectrometry (n = 449, randomized subsample of the Gothenburg part of MrOS) after hydrolysis of the conjugates with β-glucuronidase as previously described (11, 12). Interassay CV was less than 10% for all steroids analyzed. Urine samples were spot collections (before 0900 h).

Serum/plasma levels of SHBG, insulin, and glucose

SHBG was measured using immunoradiometric assay (Orion Diagnostics, Espoo, Finland) with interassay CV of 7%. Fasting serum insulin was measured with an immunometric method based on chemiluminescence technology on an ADVIA Centaur (Bayer AB, Göteborg, Sweden) with interassay CV of less than 10%. Fasting plasma glucose was quantitated by an enzymatic method on a Modular (Roche, Stockholm, Sweden) with an interassay CV of less than 4%. Homeostasis model assessment (HOMA) index was calculated as the product of fasting serum insulin level (micro-units per milliliter) and fasting plasma glucose level (millimoles per liter) divided by 22.5.

Genetic polymorphism analysis

Genotyping of the UGT2B15 $D^{85}Y$ (rs 1902023) single nucleotide polymorphism and the UGT2B17 deletion polymorphism was performed as previously described (4, 5, 13). Due to massive manual workload [separation on gel for the deletion (Del) detection], the UGT2B17 deletion polymorphism was analyzed in only a subsample (n = 615, subjects with DNA available and starting from the last recruited subject) of the young adult male cohort; only those not found in the assay detecting the intact UGT2B17 gene [wild-type (WT)] were chosen for UGT2B17 homozygous Del allele identification.

Statistical analysis

Existence of Hardy-Weinberg equilibrium was tested using χ^2 analysis. Linkage disequilibrium between the two polymorphisms was calculated by a likelihood ratio test using the genetic analysis package (version 1.0-9) and LD function of the R 2.4.0 program (www.r-project.org). Differences in serum and urinary sex steroid and metabolite levels between the different genotypes (DD, DY, and YY; and Del/Del, Del/WT, and WT/WT) were compared by ANOVA, followed by Tukey's *post hoc* test. The independent predictive value of the UGT2B15 $D^{85}Y$ and the UGT2B17 deletion polymorphisms for parameters reflecting body composition and serum parameters were investigated using linear regression analyses including age as covariate.

Results

Allele frequencies for D and Y in the UGT2B15 $D^{85}Y$ polymorphism were 0.47 and 0.53, respectively, in the young adult men and 0.45 and 0.55, respectively, in the elderly men. For the UGT2B17 deletion polymorphism, allele frequencies were 0.31 for the deletion and 0.69 for the WT allele in the elderly men. Neither in the young adult nor in the elderly men did χ^2 analyses show any deviation from Hardy-Weinberg equilibrium for any of the polymorphisms. The results from the linkage disequilibrium analysis showed no evi-

TABLE 1. The UGT2B17 deletion and the UGT2B15 $D^{85}Y$ polymorphisms as predictors of sex steroids and SHBG in elderly men

	All subjects	UGT2B17 deletion				UGT2B15 $D^{85}Y$			
		Del/Del	Del/WT	WT/WT	*P* value	DD	DY	YY	*P* value
Serum parameters		(n = 77)	(n = 432)	(n = 444)		(n = 213)	(n = 492)	(n = 271)	
T (ng/ml)	4.43 ± 1.87[a]	4.07 ± 1.84	4.37 ± 1.82	4.55 ± 1.91	NS	4.64 ± 2.00	4.42 ± 1.92	4.31 ± 1.69	NS
DHT (ng/ml)	0.35 ± 0.19[a]	0.32 ± 0.17	0.36 ± 0.21	0.36 ± 0.19	NS	0.37 ± 0.21	0.35 ± 0.20	0.35 ± 0.17	NS
Androsterone-G (ng/ml)	33.3 ± 67.1[a]	26.8 ± 19.5	36.2 ± 98.2	31.1 ± 24.0	NS	33.1 ± 29.0	33.3 ± 90.4	32.2 ± 31.7	NS
Androstanediol-3G (ng/ml)	1.50 ± 2.24	1.31 ± 0.88	1.61 ± 3.18	1.40 ± 1.02	NS	1.51 ± 1.17	1.47 ± 2.89	1.48 ± 1.44	NS
Androstanediol-17G (ng/ml)	2.64 ± 2.47[a]	1.64 ± 1.27[c]	2.86 ± 3.16[b]	2.61 ± 1.76[b]	<0.001	3.20 ± 2.03[b,c]	2.64 ± 2.59[b]	2.15 ± 2.48[c]	<0.001
SHBG (nmol/liter)	47.3 ± 24.7[a]	44.5 ± 18.4	49.1 ± 26.3	46.0 ± 23.9	NS	45.8 ± 22.8	48.3 ± 25.9	46.8 ± 23.4	NS
Urine parameters		(n = 34)	(n = 227)	(n = 181)		(n = 88)	(n = 227)	(n = 134)	
T (ng/μmol creatinine)	1.88 ± 1.19	0.15 ± 0.10[c]	1.89 ± 1.05[b]	2.22 ± 1.22[b]	<0.001	1.91 ± 1.09	1.80 ± 1.23	2.03 ± 1.21	NS
T/epitestosterone	1.02 ± 0.76	0.08 ± 0.04[c]	1.05 ± 0.78[b]	1.17 ± 0.69[b]	<0.001	1.05 ± 0.72	0.97 ± 0.82	1.09 ± 0.69	NS
DHT (ng/μmol creatinine)	0.34 ± 0.29	0.20 ± 0.27[c]	0.35 ± 0.30[b]	0.35 ± 0.28[b]	0.015	0.39 ± 0.30	0.34 ± 0.32	0.28 ± 0.21	NS

Values are given as means ± SD. Serum hormone levels were compared by Student's *t* test and *P* values by ANOVA. G, Glucuronide; NS, nonsignificant.

[a] $P < 0.05$ *vs.* young adult men.

[b] $P < 0.05$ *vs.* Del/Del for UGT2B17 deletion and $P < 0.05$ *vs.* YY for UGT2B15 $D^{85}Y$.

[c] $P < 0.05$ *vs.* Del/WT for UGT2B17 deletion and $P < 0.05$ *vs.* DY for UGT2B15 $D^{85}Y$.

dence of linkage between the UGT2B15 $D^{85}Y$ and the UGT2B17 deletion polymorphisms.

Serum and urine analyses

Serum levels of the glucuronidated androgen metabolite androstanediol-17-glucuronide, but not those of androstanediol-3-glucuronide or androsterone-glucuronide, were associated with the UGT2B17 deletion polymorphism in both elderly and young adult men (Tables 1 and 2). Androstanediol-17-glucuronide levels were lower for subjects with the Del/Del genotype than for subjects with the Del/WT and the WT/WT genotypes. The UGT2B17 deletion polymorphism was strongly associated with the urinary levels of T and moderately associated with urinary DHT (Table 1). Both urinary T and DHT were lower for the Del/Del subjects than for the Del/WT and WT/WT subjects (Table 1). Furthermore, the urinary T to epitestosterone ratio was strongly associated with the UGT2B17 deletion polymorphism.

Androstanediol-17-glucuronide levels were clearly associated with the UGT2B15 $D^{85}Y$ polymorphism in both young adult and elderly men (Tables 1 and 2). The serum levels of androstanediol-17-glucuronide were higher for subjects with the DD and the DY genotypes than for subjects with the YY genotype. Serum DHT and SHBG levels but not T levels were slightly higher for the DD than for the YY genotype in the young adult men (Table 2).

Body composition analyses

Several indicators of body fat (body weight, body mass index, total body fat, and trunk fat; $P < 0.05$) were associated with the UGT2B17 deletion polymorphism in the elderly cohort and with the UGT2B15 $D^{85}Y$ polymorphism in the young adult cohort (Table 3). Some of the parameters reflecting fat mass (total body fat percent and arm fat; $P < 0.05$) were associated with the UGT2B15 $D^{85}Y$ polymorphism also in the elderly cohort. Subjects with the UGT2B15 YY genotype had a higher amount of fat than the subjects with the DY and DD genotypes, and subjects with the UGT2B17 Del/Del genotype had a higher amount of fat than the subjects with the Del/WT and WT/WT genotypes (Table 3; $P < 0.05$). In addition, the UGT2B17 deletion polymorphism was a predictor of serum insulin and HOMA index in the elderly cohort (Table 3; $P < 0.05$).

Discussion

We here demonstrate that both the UGT2B15 $D^{85}Y$ polymorphism and the UGT2B17 deletion polymorphism have an impact on the glucuronidation pattern of androgens/androgen metabolites.

The present *in vivo* data, showing that the UGT2B15 $D^{85}Y$ polymorphism is strongly associated with serum levels of androstanediol-17-glucuronide but not androstanediol-3-glucuronide or androsterone-glucuronide (Fig. 1) support earlier *in vitro* findings that UGT2B15 specifically conjugates the 17β-hydroxy position of androstanediol (14). Furthermore, the results indicate that the G to T polymorphism in the *UGT2B15* gene is functional. Because the serum levels of androstanediol-17-glucuronide were higher in the DD than in the YY subjects, we conclude that subjects with the DD genotype probably have a more efficient UGT2B15 enzyme for 17-glucuronidation of androstanediol than the YY subjects.

Earlier *in vitro* studies have indicated that UGT2B17 has the capacity to glucuronidate androstanediol at the 17β-hydroxy position (resulting in androstanediol-17-glucuronide) and androsterone at the 3α-hydroxy position (resulting in androsterone-glucuronide) (2). However, the present *in vivo* study of a naturally occurring gene inactivation of the *UGT2B17* gene demonstrates that UGT2B17 is a rather selective enzyme in the glucuronidation of androgen metabolites, enhancing the 17β-glucuronidation of androstanediol but not the 3α-glucuronidation of androstanediol or androsterone (Fig. 1).

UGTs glucuronidate not only androgen metabolites but also T and DHT. The present finding of a major role of UGT2B17 for T excretion in elderly men (Fig. 1) confirms our previous results in young adult men (13) and is consistent with previous *in vitro* reports showing that T is a good substrate for UGT2B17 (15) but not for UGT2B15 (2). In addition, the present finding that urine DHT was associated with the UGT2B17 deletion polymorphism but not with the UGT2B15 $D^{85}Y$ polymorphism (Fig. 1) is supported by previous studies investigating enzymatic activity *in vitro* (2, 14). Interestingly, the clear association between the UGT2B15 $D^{85}Y$ polymorphism and androstanediol-17-glucuronide levels was accompanied by slightly affected serum levels of SHBG and DHT in the young adult men, suggesting that this polymorphism might affect androgen-dependent phenotypes. The mechanism behind the affected SHBG levels in the young adult

TABLE 2. The UGT2B17 deletion and the UGT2B15 $D^{85}Y$ polymorphisms as predictors of sex steroids and SHBG in young adult men

Serum parameters	All subjects	UGT2B17 deletion			UGT2B15 $D^{85}Y$			
		Del/Del (n = 46)	Del/WT + WT/WT (n = 569)	*P* value	DD (n = 222)	DY (n = 535)	YY (n = 304)	*P* value
T (ng/ml)	4.69 ± 1.52	4.76 ± 1.53	4.81 ± 1.46	NS	4.87 ± 1.63	4.72 ± 1.53	4.53 ± 1.38	NS
DHT (ng/ml)	0.31 ± 0.11	0.31 ± 0.12	0.31 ± 0.11	NS	0.31 ± 0.11	0.31 ± 0.12[a]	0.29 ± 0.10[b]	0.048
Androsterone-G (ng/ml)	61.2 ± 35.4	61.7 ± 28.8	63.0 ± 35.8	NS	60.4 ± 39.8	63.2 ± 35.1	58.5 ± 32.6	NS
Androstanediol-3G (ng/ml)	1.52 ± 0.92	1.58 ± 0.81	1.58 ± 0.98	NS	1.49 ± 0.86	1.54 ± 0.96	1.51 ± 0.90	NS
Androstanediol-17G (ng/ml)	4.03 ± 2.08	3.28 ± 2.13	4.16 ± 2.09[a]	<0.001	4.69 ± 2.22[a]	4.27 ± 2.06[a]	3.13 ± 1.67[b]	<0.001
SHBG (nmol/liter)	20.4 ± 7.4	20.4 ± 6.9	20.1 ± 7.0	NS	21.9 ± 7.6[a,b]	20.5 ± 7.6[a]	19.1 ± 6.7[b]	<0.001

Values are given as means ± SD. Serum hormone levels were compared by Student's *t* test and *P* values by ANOVA. G, Glucuronide; NS, nonsignificant.

[a] $P < 0.05$ *vs.* Del/Del for UGT2B17 deletion and $P < 0.05$ *vs.* YY for UGT2B15 $D^{85}Y$.

[b] $P < 0.05$ *vs.* Del/WT for UGT2B17 deletion and $P < 0.05$ *vs.* DY for UGT2B15 $D^{85}Y$.

TABLE 3. The UGT2B17 deletion and the UGT2B15 $D^{85}Y$ polymorphisms as predictors of body composition and metabolic serum parameters in men

	Elderly men					Young adults				
	Mean ± SD	UGT2B17 deletion		UGT2B15 $D^{85}Y$		Mean ± SD	UGT2B17 deletion		UGT2B15 $D^{85}Y$	
		β	P	β	P		β	P	β	P
Height (cm)	175.7 ± 6.4	−0.01	0.66	0.01	0.62	181.4 ± 6.7	−0.04	0.36	0.05	0.095
Weight (kg)	80.9 ± 12.2	−0.10	0.002	0.01	0.36	73.8 ± 11.9	−0.03	0.51	0.08	0.01
BMI (kg/m^2)	26.2 ± 3.5	−0.11	0.001	0.01	0.47	22.4 ± 3.2	−0.01	0.81	0.06	0.049
DXA										
Total body lean (kg)	59.3 ± 6.7	−0.09	0.008	−0.00	0.96	57.4 ± 6.2	0.00	0.92	0.05	0.097
Total body fat (kg)	18.5 ± 5.7	−0.09	0.007	0.05	0.11	13.4 ± 8.0	−0.01	0.78	0.07	0.035
Total body fat %	23.4 ± 5.0	−0.07	0.049	0.07	0.028	17.2 ± 7.4	−0.01	0.74	0.05	0.083
Arm fat (kg)	1.06 ± 0.37	−0.07	0.048	0.07	0.044	0.56 ± 0.41	−0.04	0.31	0.06	0.063
Trunk fat (kg)	9.67 ± 3.56	−0.10	0.004	0.04	0.169	6.76 ± 4.31	−0.02	0.66	0.06	0.050
Central fat distribution (%)	51.3 ± 6.2	−0.08	0.022	0.01	0.79	49.8 ± 4.5	0.02	0.66	0.00	0.998
Metabolic serum/plasma parameters										
Glucose (mmol/liter)	5.8 ± 1.5	−0.05	0.15	−0.02	0.61	ND	ND		ND	
Insulin (μU/ml)	10.6 ± 11.2	−0.08	0.033	−0.02	0.62	ND	ND		ND	
HOMA index	2.9 ± 4.0	−0.08	0.028	−0.02	0.66	ND	ND		ND	

Parameters were investigated using linear regression, including age as covariate. Subjects with known diabetes mellitus were excluded from the regression analysis regarding insulin, glucose, and HOMA index. The UGT2B17 deletion polymorphism is coded as WT/WT > Del/WT > Del/Del. The UGT2B15 $D^{85}Y$ polymorphism is coded as YY > DY > DD. Standardized β and P values are presented. Central fat distribution is calculated as trunk fat/total body fat × 100. ND, Not determined.

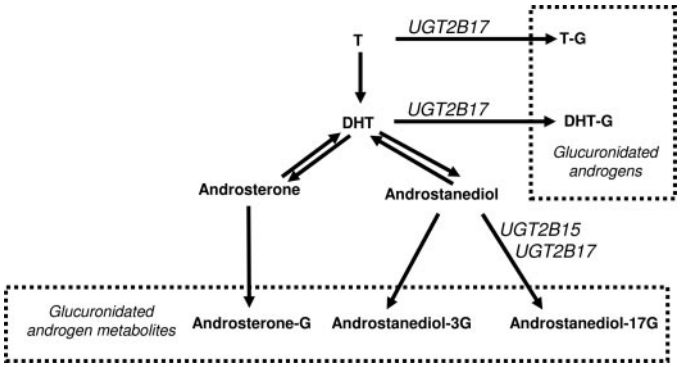

FIG. 1. Pathway diagram demonstrating the specificity *in vivo* of the glucuronidation capacity of UGT2B17 and UGT2B15 as suggested by the results from the present study in men. Our findings indicate that UGT2B17 is involved in 17-glucuronidation of mainly T but also of DHT and androstanediol, whereas UGT2B15 is involved in the 17-glucuronidation of androstanediol. Hence, the UGT2B15 $D^{85}Y$ and the UGT2B17 deletion polymorphisms might have an impact on the local androgen/androgen metabolite levels in fat tissue and/or other tissues of importance for fat homeostasis and thereby affect fat mass. However, additional functional studies are required to determine how these two polymorphisms are linked to the regulation of fat mass. G, Glucuronide.

cohort is unknown, but one may speculate that the UGT2B15 $D^{85}Y$ polymorphism affects the local androgenic environment in selected tissues, which in turn results in a regulation of SHBG levels. However, one cannot exclude a direct influence on SHBG abundance, which secondarily changes androgen metabolism.

Several measures of fat mass were associated with the UGT2B15 $D^{85}Y$ polymorphism in both the young adult and the elderly men and with the UGT2B17 deletion polymorphism in the elderly men (Fig. 1), suggesting that these two UGTs, with the capacity to alter the local androgenic environment, might affect fat mass homeostasis. In contrast, the UGT2B17 deletion polymorphism was not associated with fat mass in the young adult men, indicating that the impact of this polymorphism on fat mass either is age dependent or of inconsistent nature.

It is impossible from this association study to determine the causality of the association between the polymorphisms and fat mass. Because UGT2B15 is highly expressed in adipose tissue (16), one may speculate that a substantial part of the UGT2B15 activity is adipose tissue derived and/or that the UGT2B15 $D^{85}Y$ polymorphism affects local androgen/androgen metabolite levels in adipose tissue, which in turn affects the fat mass. In contrast to UGT2B15, no major expression of UGT2B17 has been described in fat tissue (16). The UGT2B17 deletion polymorphism, but not the UGT2B15 $D^{85}Y$ polymorphism, was associated not only with fat mass but also with insulin sensitivity, indicating that the metabolic consequences of these two polymorphisms at least partly differ.

In conclusion, The UGT2B15 $D^{85}Y$ and the UGT2B17 deletion polymorphisms are predictors of the glucuronidation pattern of androgens/androgen metabolites. Our findings indicate that UGT2B17 is involved in 17-glucuronidation of mainly T but also of DHT and androstanediol and that UGT2B15 mainly is involved in the 17-glucuronidation of androstanediol. Furthermore, these two polymorphisms are predictors of fat mass in men. Additional studies are required to determine the clinical significance of the reported associations between the UGT2B15 $D^{85}Y$/UGT2B17 deletion polymorphisms and glucuronidation patterns of androgens because this cannot be determined by the present investigation.

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