

Large Differences in Testosterone Excretion in Korean and Swedish Men is Strongly Associated with an UDP-Glucuronosyl Transferase 2B17 Polymorphism

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Abbreviated Title: UGT2B17 deletion and urinary testosterone

Key Terms: UGT2B17; Ethnic Variation; Testosterone glucuronidation; Urinary excretion

Word Count: Text: 3389

Tables: 2

Figures: 3

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Grants or Fellowships: This work was supported by grants from the World Anti-Doping Agency (WADA) and from the Swedish Cancer Society.

Abbreviations: UGT, uridine diphosphoglucuronosyl-transferase; SHBG, sex hormone binding globulin; del, deletion; ins, insertion; T, testosterone; NST, non-SHBG bound testosterone; 17OHP, 17 α -hydroxyprogesterone; PCR, polymerase chain reaction; HPLC, High pressure liquid chromatography; UDPGA, UDP-glucuronic acid; DHT, dihydrotestosterone; Cr, creatinine.

Abstract

Context: The reproductive endocrinology in Asians and Caucasians is of great interest in view of large differences in prostate cancer rate and sensitivity to pharmacological male contraception. In addition, interpretation of certain anti-doping tests is confounded by inter-ethnic variation in androgen disposition.

UDP-glucuronosyl transferases have a key role in the homeostasis and metabolism of androgens. Recently a deletion polymorphism was detected in the *UGT2B17* gene.

Objective: To evaluate the contribution of the *UGT2B17* deletion polymorphism to the inter-individual and inter-ethnic variation of androgen metabolism and excretion.

Methods and Results: Urine from 122 Swedish and 74 Korean healthy men were analyzed for several androgen glucuronides including testosterone. The distribution of the natural logarithms of urinary testosterone concentrations showed a distinct bimodal pattern in both groups, suggesting a monogenic inheritance.

When the *UGT2B17* genotypes were compared with urinary testosterone levels all of the individuals of the *UGT2B17* homozygous del/del genotype had no or negligible amounts of urinary testosterone. The del/del genotype was 7 times more common in the Korean (66.7 %) than in the Swedish population (9.3 %). In addition, the Swedes had significantly higher levels of serum testosterone compared to the Koreans.

Conclusions: Our results show that the *UGT2B17* polymorphism is strongly associated with the bimodal distribution of the testosterone excretion and also with the large differences in testosterone excretion between Koreans and Swedes.

Introduction

A number of conspicuous interethnic differences between Asian and Caucasian men in reproductive endocrinology are still lacking an explanation (see van Houten and Gooren (1) for a review). For example, the rate of prostate cancer is 2-40 times higher among Caucasian than Asian men (2). Differences between these groups in sensitivity to male contraception regimens have also been described. Thus, Asian men respond to exogenous contraceptive androgens with a higher suppression of spermatogenesis than Caucasian men (3, 4). It is also established that the urinary testosterone/*epi*-testosterone ratio, commonly used in international anti-doping test programs, is considerably lower in Asians than in Caucasians leading to difficulties in interpretation of the results. The limited effect of androgen doping on testosterone excretion in Asian populations increases the risk of false-negative results (5).

Much of the current interest in androgen research is focused on the role of testosterone in prostate cancer (6) and on the detection and effects of doping in order to improve the physical achievements in sports (7). Whereas relatively much is known about the function of testosterone and its effects in target organs, little is known about its disposition including urinary excretion.

Testosterone is excreted mainly as glucuronide conjugates (8) following glucuronidation by UDP-glucuronosyl transferases (UGT). These enzymes have a key role in the homeostasis of a number of endogenous molecules including steroid hormones (9), and they facilitate their excretion in bile and urine (9). There are 7 members of the UGT2B sub-family. They have a preference for glucuronidation of bile acids, steroids, fatty acids, carboxylic acids, phenols and carcinogens (9-11). One of these, UGT2B17, was found to be particularly active in androgen glucuronidation (12).

A gene deletion in this enzyme gene was recently described (13) and it was further characterized by Wilson *et al* (14). The physiological consequences of this deletion polymorphism are unknown.

Given this background we decided to study the urinary excretion pattern and circulating concentrations of testosterone and other androgens in relation to the UGT2B17 genetic polymorphism in non-athlete volunteers of Caucasian and Asian ethnic descent. Our results show that this polymorphism is strongly associated with the bimodal distribution of the testosterone excretion as well as the large differences in androgen excretion between Asians and Caucasians. These data may have relevance for understanding the mechanisms behind prostate disease, and are of great importance for the anti-doping test programs.

Materials and Methods

Study population and sample selection

Seventy-four unrelated Korean male subjects 21 – 39 yrs (mean 26.3 ± 3.5 yrs) were recruited among medical students and personnel at Inha University Hospital, Incheon, Korea. Their health status was assessed by medical questionnaire. All subjects in this study participated voluntarily after giving informed consent. The study was approved by the Institutional Review Board at Inha University Hospital and by the Ethics Committee at the Karolinska University Hospital. The Caucasian sample included 122 men; age 18.0-20.1 yrs (mean 18.9 ± 0.6 yrs), that were randomly selected from the *Gothenburg Osteoporosis and Obesity Determinants (GOOD)* study, which was initiated with the aim to determine both environmental and genetic factors for bone and fat mass, where study subjects were randomly identified using national population registers, contacted by telephone, and asked to participate in this study. That study was approved by the Ethics Committee at Gothenburg University and written informed consent was obtained from all participants.

Serum, Plasma and Urine

In the Korean population venous blood was obtained from the cubital vein and collected in EDTA tubes (for DNA and plasma extraction). Plasma was immediately extracted at 4°C and kept frozen at -20°C until analysis. In the Swedish population whole blood was obtained from the cubital vein and collected in EDTA tubes (for DNA extraction) and in gel-containing tubes (for serum extraction). Serum was extracted using standardized procedures, immediately frozen and stored at -80°C until analysis. The serum and plasma samples were analysed in the same lab using the same assay and according to the manufacturer of the immunoassay kit for steroid analyses in the circulation (Orion Diagnostica, Espoo, Finland) identical results are obtained in serum and plasma.

Spot urine samples were collected and immediately frozen at -20°C. To minimise any influence of diurnal variation all blood and urine samples were collected between 2 pm and 7.30 pm.

Urinary steroids

Urinary unconjugated steroids (typically < 1 % of glucuronide fraction) + steroid glucuronides were determined by gas chromatography – mass spectrometry after hydrolysis of the conjugates with β -glucuronidase as described (15) with minor modifications (16). Within and between assay coefficients of variation were < 7 % and < 10 % for all steroids analyzed.

Serum and Plasma Testosterone, SHBG and 17 α -OH Progesterone assays

Testosterone (T) was measured by Spectria [125I] Coated Tube Radioimmunoassay, and sex hormone-binding globulin (SHBG) was measured by [125I] Immunoradiometric Assay (“IRMA”; Orion Diagnostica, Espoo, Finland). Non SHBG-bound T (NST, sum of unbound + albumin-bound testosterone) was used as an index of biologically active testosterone as proposed by Pardridge (17). Apparent concentrations of NST were calculated from values for total testosterone, SHBG and a fixed albumin concentration of 42 g/L by successive approximation using a computer program based upon an equation system derived from the law of mass action (18). Additional analysis of 17 α -hydroxyprogesterone (17OHP) was performed in sub-groups of the populations consisting of 29 Koreans and 22 Swedes by competitive radioimmunoassay using a commercial kit obtained from CIS Bio International, Gif-sur-Yvette, France (“OHP-CT”). Detection limits, and within, and between assay coefficients of variation were for testosterone 0.1 nmol/L, 5.5 % and 5.8 %, for SHBG 1.3 nmol/L, 2.5 % and 6.9 % and for 17OHP 0.1 nmol/L, 7.8 % and 10.0 % respectively.

All the serum and plasma samples were analysed in the same laboratory to avoid inter-assay variation.

Genotyping of the UGT2B17 deletion

Genotyping was essentially performed as previously described (14). The deletion specific primers (J-markers) and the Exon 6 specific primers were used in a standard PCR-protocol (AmpliTaq®DNA Polymerase, Applied Biosystems) and the products were identified in a 2 % agarose gel. Due to low DNA concentrations, some of the Swedish samples were analysed with SYBR®GREEN Master Mix (Applied Biosystems) and the product formations was followed on an ABI Prism®7700. Additionally these products were also confirmed on a gel. DNA samples from heterozygous individuals “del/ins”, a product from both the reactions appeared, whereas individuals homozygous for the deletion allele “del/del”, and individuals homozygous for UGT2B17 insertion allele “ins/ins” only one product was observed with either the deletion specific primers or the Exon 6 primers.

The number of subjects with DNA samples available for genotyping was 66 Koreans and 86 Swedes.

HPLC analysis of testosterone glucuronidation in human liver microsomes

Seventeen human liver tissue samples and DNA were obtained from 14 Caucasian and 3 Asian human donor livers. The donor samples were genotyped as previously described, and microsomes were prepared according to standard procedure (19).

The microsomes were stored in 50 mM potassium phosphate buffer (pH 7.4) at -80°C until use.

The protein concentration was determined spectrophotometrically according to Lowry *et al.* (20).

Incubation samples were performed in duplicates as described by Narayanan *et al.* (21) using 75 μ M testosterone as a substrate and 2.5 mM UDPGA as co-factor. The incubation was stopped by addition of 100 μ l acetonitrile. The mixture was vortexed and centrifuged at 14,000 rpm for 5 min. The supernatant was removed and 20 μ l injected onto a Zorbax SB-CN column (150 \times 4.6 mm I.D, 5 μ m, Agilent Technologies, CA, USA). The mobile phase consisted of acetonitrile-50 mM ammonium phosphate buffer, pH 4.5 (30:70).

Peak areas of glucuronide were calculated using a calibration curve that was prepared for each experiment using glucuronide standard solutions. Enzyme activity was expressed as reaction velocity by dividing the amount of product formed by the incubation time and microsomal protein content (nmoles/ mg per min). The between assay coefficient of variation was < 9 %.

Data analyses

The between-subject variability in urine dilution was corrected for by dividing the concentration values by the urinary creatinine (Cr) concentration. All urinary values are expressed as the unconjugated (typically < 1 % of glucuronide fraction) + the glucuronide conjugated fraction after correction for creatinine. When the data was not normally distributed the data is presented as the median with the 25th and 75th percentiles in parenthesis.

Comparisons of hormonal levels were performed according to distribution with Student's two-tailed t-test or the Mann-Whitney U-test. For categorical variables the chi-square test was used.

Results

Urinary steroids and ethnicity

The median value of testosterone excretion was 16 times higher in the Swedish population (5.4 (3.7-7.1) ng/ μ mol Cr) than the Korean population (0.33 (0.25-0.58) ng/ μ mol Cr). The *epi*-testosterone concentrations did not differ between the ethnic groups. Most precursors and metabolites of testosterone investigated were significantly higher in the Swedes, with the exception for etiocholanolone, which was significantly higher in the Koreans (Table 1a).

Interestingly 5 β -androstane-3 α ,17 β -diol excretion was 2.7 times higher in Swedes than in Koreans whereas no difference was found for 5 α -androstane-3 α ,17 β -diol. There were no differences between the ethnic groups in creatinine excretion.

The distribution of the natural logarithms of urinary testosterone/Cr concentrations showed a distinct bimodal pattern in both the Korean and the Swedish population (Fig 1a). However, the distribution into the low and high excretion mode differed markedly. In Koreans, 74.3 % and in Swedes 6.6 % belonged to the low urinary testosterone excretion group, whereas 25.7 % and 93.4 % of the Koreans and Swedes belonged to the high testosterone excretion group. The urinary concentrations of androgens in the low and high testosterone excretion groups are listed in Table 1b.

Serum testosterone, SHBG and ethnicity

Compared to the Koreans, the Swedish population had significantly higher concentrations of total testosterone (18.0 \pm 5.3 vs. 14.4 \pm 4.6 nmol/L, $p < 0.001$) and SHBG (20.2 \pm 6.2 vs. 18.2 \pm 6.2 nmol/L, $p = 0.030$). The non-SHBG bound testosterone (NST) also differed significantly between the two ethnic groups; (13.4 \pm 3.9 for Swedes and 10.8 \pm 3.2 for Koreans ($p < 0.001$)) (Fig 1b).

The NST correlated with the urinary testosterone both in Swedes ($r = 0.35$, $p < 0.001$) and in Koreans ($r = 0.39$, $p < 0.001$). Similarly, total testosterone correlated significantly with SHBG in both Swedes ($r = 0.28$, $p = 0.002$) and Koreans ($r = 0.52$, $p < 0.001$).

UGT2B17 deletion genotypes

We screened 66 of the Koreans and 86 of the Swedes for presence or absence of the *UGT2B17* gene. The results in Table 2 show that the distribution of the genotypes was significantly different between these two ethnic groups (H_0 , test for independence between genotype and ethnic background; $\chi^2 = 57.5$, 2 *df*, $p < 0.001$). The del/del genotype is 7.2 times more common among the Koreans than the Swedes (66.7 and 9.3 %, respectively).

All of the Koreans and Swedes with the del/del genotype had unmeasurable or negligible amounts of urinary testosterone (Fig 2, left panel). The genotype also significantly affected the excretion of DHT (Fig 2, right panel), although a large part of the samples (25 % in the del/del, 26 % in the ins/del and 10 % in the ins/ins group) had DHT glucuronide levels below the detection limit. The proportion of the samples that had unmeasurable levels of DHT was similar in both ethnic groups.

Serum hormones and genotype

In the subgroup analysed for 17OHP the levels of this steroid were significantly lower in the Korean del/del individuals (2.0 ± 0.7 , $n = 19$) than the combined ins/del and ins/ins Koreans (2.7 ± 0.9 , $n = 10$) ($p = 0.027$) and non-significantly reduced in the del/del Swedes (3.3 ± 1.3 , $n = 7$) compared to the combined ins/del and ins/ins Swedes (4.2 ± 1.7 , $n = 15$). The serum levels of testosterone, NST and SHBG did not differ between the genotypes of the same ethnic descent.

In vitro testosterone glucuronide formation using human liver microsomes

Among the Caucasian liver donors, 4 had the del/del genotype, 4 were ins/del and 6 belonged to the ins/ins genotype. Two of the Asian samples were del/del, while one had the ins/ins genotype. There was a significantly higher formation of testosterone glucuronide in human liver microsomes having one or two copies of the *UGT2B17* gene compared to microsomes with the del/del genotype ($p = 0.038$) (Fig 3). There was no difference in glucuronidation rate between the ins/del and the ins/ins genotype, or between the ethnic groups within the same genotype.

Discussion

This work provides a genetic correlate for the conspicuous and large difference in testosterone excretion between Caucasians and Asians. We show for the first time that both Asian and Caucasian men can be divided into two subgroups according to their urinary testosterone levels (Fig 1a). The bimodal distribution suggests a monogenic inheritance pattern. This assumption is strongly supported by our results, as all of the individuals of the *UGT2B17* homozygous del/del genotype had no or negligible amounts of testosterone in their urine. This genotype is devoid of the enzyme gene (13, 14). There were three Asian individuals that were heterozygotes and one Asian that was homozygous for the ins/ins, yet they had negligible amounts of urinary testosterone. We have no explanation for this, but the possibility of other functional mutations in the *UGT2B17* gene cannot be ruled out. Absence of the *UGT2B17* gene was 7 times more common in the Korean than the Swedish population sample.

It has been suggested that the low concentration of testosterone in male urine is a result of its rapid and complete conversion to the ultimate urinary metabolites (androsterone and etiocholanolone) due to higher specific enzyme activity towards testosterone (22). However, our results show that the low urinary testosterone excretion group, in addition to significantly lower levels of androsterone, also had significantly lower amounts of several investigated urinary testosterone metabolites (table 1b). Thus, it is conceivable that the low excretion is due to slow formation of androgen glucuronides.

We did not measure the glucuronidated fraction of testosterone in serum, but this fraction is also likely to be lower in the Korean population considering the low urinary levels of testosterone glucuronide.

The serum levels of total testosterone, SHBG and NST were also significantly higher in Caucasians, although the difference was not as large as for the urinary levels (Fig 1b). The method used for calculating NST (17, 18) also enables the calculation of free testosterone.

Recently it was shown that the method may overestimate the concentration of *free testosterone*, when compared to values measured by physicochemical methods (23). However, as far as we know from the literature, no corresponding comparisons have been undertaken for NST.

Comparative studies on plasma levels of androgens in Asians and Caucasians have generated inconsistent results. Most investigators were unable to demonstrate a difference in serum concentrations of bioavailable testosterone (24-26), while one group (27) found even higher serum testosterone levels in Chinese men compared to Caucasians. In contrast, de Jong *et al.* (28) and Heald *et al.* (29) found a slight difference consistent with our findings. Lower levels of testosterone metabolites such as androsterone glucuronide and androstanediol glucuronide were observed in plasma of Asian subjects (24, 25). This finding was interpreted as a sign of lower androgen “load”, which may contribute to the lower incidence of prostate cancer in Asians. Their findings may be due to a larger proportion of UGT2B17 del/del genotypes among Asians, which we demonstrate in this work.

Seventy-five percent of circulating 17OHP is of testicular origin in healthy adult males.

Theoretically, a decreased metabolism of testosterone is compatible with normal circulating testosterone concentrations provided the testicular testosterone synthesis is reduced. Other testicular steroids, such as 17OHP, being affected by the defective metabolism would then be present at subnormal concentrations (30). Consistent with this, serum 17OHP was significantly decreased in the Korean and in the combined ethnic del/del subjects. Unfortunately we only had

access to 7 Swedish del/del samples, which makes it difficult to interpret the serum data. Further studies are needed to elucidate whether 17OHP levels and testicular activity are associated with the gene-deletion.

We found a positive correlation between serum testosterone and SHBG. This indicates that the UGT2B17 deletion does not seem to affect the hypothalamic-pituitary-testicular axis to any greater extent (31) since such a correlation was also present in the Koreans where 67 % had the del/del genotype.

We measured the glucuronidated moiety of steroids in urine. Only a minor part of the urinary testosterone is excreted as sulphate conjugates (8). However, it cannot be ruled out that there is a compensatory increase in sulphate conjugation of testosterone in subjects with low urinary testosterone. On the other hand, in a comparison of urinary sulphate and glucuronide conjugates of testosterone and *epi*-testosterone, Borts and Bowers (32) found that both the sulphate and glucuronide conjugates of testosterone were lower in a Chinese than in a Caucasian unselected population sample.

The UGT2B enzymes have a distinct, but overlapping, specificity towards different steroids (12). Turgeon *et al.* (12) compared the enzymatic activity of UGT2B4, 2B7, 2B15 and 2B17 *in vitro* towards a number of different substrates including steroids. They found that UGT2B17 showed the highest activity towards testosterone and DHT and, surprisingly also etiocholanolone. Our data are consistent with these results (12) except etiocholanolone that was not excreted at a lower rate in the del/del subjects. UGT2B15 was shown to have a low activity towards testosterone and a somewhat higher activity towards DHT (12). A D⁸⁵Y polymorphism in the UGT2B15 gene

increased the V_{\max} 2-fold for DHT and 5 α -androstane-3 α ,17 β -diol (33). The more active Y⁸⁵ allele being more common in Caucasians (32.2 %) than in Asians (18.7 %) (34). We did not study this polymorphism, but it is possible that it may have contributed to the inter-individual and inter-ethnic variation in glucuronidation of DHT and perhaps also testosterone. On the other hand, the urinary levels of 5 α -androstane-3 α ,17 β -diol, which is one of the major substrates of UGT2B15, were equal in Koreans and Swedes. Hence, it is unlikely that the UGT2B15 D⁸⁵Y polymorphism had any considerable impact on our results.

Further support that the UGT2B17 del/del genotype is associated with a compromised testosterone conjugation capacity was obtained in our *in vitro* experiments using human liver microsomes (Fig 3). We found that the del/del genotype was associated with a significantly lower glucuronidation rate. The residual basal rate of glucuronidation in the del/del genotype specimens may be explained by the presence of other UGT enzymes with testosterone glucuronidating activity *in vitro* (35) but with lower quantitative importance than UGT2B17.

Interestingly the UGT2B17 protein has been shown to have a more rapid turnover than other UGT2B enzyme proteins (12), which may have affected our results.

Our *in vitro* experiments demonstrating a basal rate of testosterone glucuronidation in the del/del genotype may seem inconsistent with the unmeasurable or negligible levels of glucuronide conjugated testosterone in urine of the del/del subjects. However, it is important to note that the mutual contribution to the testosterone glucuronidation of the liver and extra-hepatic organs, such as the prostate is unknown.

It is conceived that androgens play a pivotal role in prostate carcinogenesis. Therefore, androgen deprivation by inhibition of their synthesis and/or receptor interaction (36, 37) is the mainstay in treatment of prostate cancer. Environmental (38) and dietary (39) factors may explain only a minor

part of the large difference in prostate cancer incidence between Asians and Caucasians (2). As the UGT2B17 del/del genotype subjects had negligible levels of testosterone in their urine, this enzyme seems to be the most important one for testosterone glucuronidation *in vivo*. The genetic influence on glucuronidation activity in steroid target organs has not been studied. However, it is likely that genetically polymorphic testosterone glucuronidation is present in the basal cells of the prostate, where UGT2B17 appears to be one of the most important glucuronic acid conjugating enzymes (40). Thus, the UGT2B17 deletion is important to study in relation to prostate cancer rate.

In conclusion, the UGT2B17 deletion polymorphism, which is 7.2 times more common in our Asian compared to our Caucasian population sample group, provides a monogenic explanation for the low urinary testosterone excretion in Asian populations. A direct consequence of this is that the commonly used testosterone/*epitestosterone* ratio, used to detect testosterone abuse would be more useful if taking the genetic constitution into account, particularly in Asians as the del/del trait is extremely common in this group. The importance of the polymorphism for the risk of prostate cancer is uncertain, but certainly warrants further investigations.

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Table 1 Urinary levels (ng/ μ mol Creatinine) of the glucuronidated + unconjugated fraction of androgen metabolites in healthy men divided by

a) ethnic descent

	Koreans (n = 74)	Swedes (n = 122)
T/EpiT ratio	0.15 (0.08-0.68)	1.8 (1.0-2.6)***
4-Androstenedione	0.13 (0.09-0.17)	0.32 (0.22-0.45)***
5-androstene-3 β ,17 α -diol	4.4 (3.2-6.7)	6.7 (5.1-8.8)***
Testosterone	0.33 (0.25-0.58)	5.4 (3.7-7.1)***
Epitestosterone	3.0 (1.9-4.1)	3.4 (2.0-5.0)
Dihydrotestosterone	0.50 (0.23-0.80)	1.2 (0.64-1.8)***
5 α -Androstanedione	0.60 (0.40-0.91)	0.96 (0.61-1.6)***
5 α -Androstane,3 α ,17 β -diol	4.9 (3.7-6.3)	4.9 (3.6-6.4)
5 β -Androstane,3 α ,17 β -diol	3.74 (2.52-5.83)	10.1 (6.2-15.2)***
Androsterone	218 (171-264)	240 (196-309)**
Etiocholanolone	119 (88.3-182)**	99.2 (57.3-158)
11 β -OH Androsterone	62.9 (48.1-94.8)	82.5 (61.5-114)***
11 β -OH Etiocholanolone	4.3 (1.56-12.5)	23.0 (6.9-40.7)***

b) low and high urinary testosterone excretion phenotypes

	Low testosterone	High testosterone
	(n = 65)	(n = 131)
T/EpiT ratio	0.11 (0.07-0.16)	1.8 (1.1-2.6)***
4-Androstenedione	0.13 (0.09-0.18)	0.30 (0.19-0.45)***
5-androstene-3 β ,17 α -diol	4.8 (3.4-6.9)	6.4 (4.8-8.7)***
Testosterone	0.29 (0.23-0.40)	5.3 (3.9-7.1)***
Epitestosterone	3.0 (1.9-4.1)	3.4 (2.0-4.8)
Dihydrotestosterone	0.43 (0.16-0.80)	1.1 (0.57-1.7)***
5 α -Androstanedione	0.61 (0.42-0.94)	0.92 (0.55-1.6)***
5 α -Androstane,3 α ,17 β -diol	4.4 (3.5-5.9)	5.2 (3.7-6.6)
5 β -Androstane,3 α ,17 β -diol	3.1 (2.4-4.1)	10.4 (6.6-16.1)***
Androsterone	220 (178-252)	243 (189-312)**
Etiocholanolone	116 (87.0-159)	108 (61.3-170)
11 β -OH Androsterone	66.0 (51.2-97.3)	79.3 (57.3-110)*
11 β -OH Etiocholanolone	4.5 (1.8-14.4)	18.4 (5.7-36.3)***

Results are medians (in ng/ μ mol Creatinine) with the 25th and 75th percentiles in parenthesis.

Low and high testosterone excretion phenotypes are explained by the bimodal excretion pattern. In Koreans, 74.3 % and in Swedes 6.6 % belonged to the low urinary testosterone excretion group, while 25.7 % and 93.4 % of the Koreans and Swedes belong to the high testosterone excretion group. * p < 0.05, ** p < 0.01, *** p < 0.001

Table 2

UGT2B17 genotype distribution

	del/del	del/ins	ins/ins
	% (n)	% (n)	% (n)
Koreans	66.7 (44)	22.7 (15)	10.6 (7)
Swedes	9.3 (8)	39.5 (34)	51.2 (44)

Figure legends

Figure 1

a) Frequency distribution of natural logarithms of urinary unconjugated + glucuronide conjugated testosterone (ng / μ M Cr) in a Korean (n = 74) (upper panel) and a Swedish (n = 122) (lower panel) population of healthy men.

b) Serum levels of non-SHBG bound testosterone (nmol/L) (left panel) and urinary unconjugated + glucuronide conjugated testosterone levels (ng / μ M Cr) (right panel) in Swedish, Koreans and in combined low and high urinary testosterone excretion phenotypes.

Figure 2

Relation between urinary unconjugated + glucuronide conjugated testosterone glucuronide (ng / μ M Cr) (left panel) and urinary unconjugated + glucuronide conjugated dihydrotestosterone (DHT) (ng / μ M Cr) (right panel) and UGT2B17 genotype in the combined Swedish and Korean population samples. Significances of differences are denoted by * = $p < 0.05$; ** = $p < 0.01$ and *** = $p < 0.001$.

Figure 3

Relation between testosterone glucuronidation rate and UGT2B17 genotype in microsomes from different human livers. Testosterone was used as a substrate and UDPGA as a co-factor. * = $p < 0.05$.

Figure 1a)

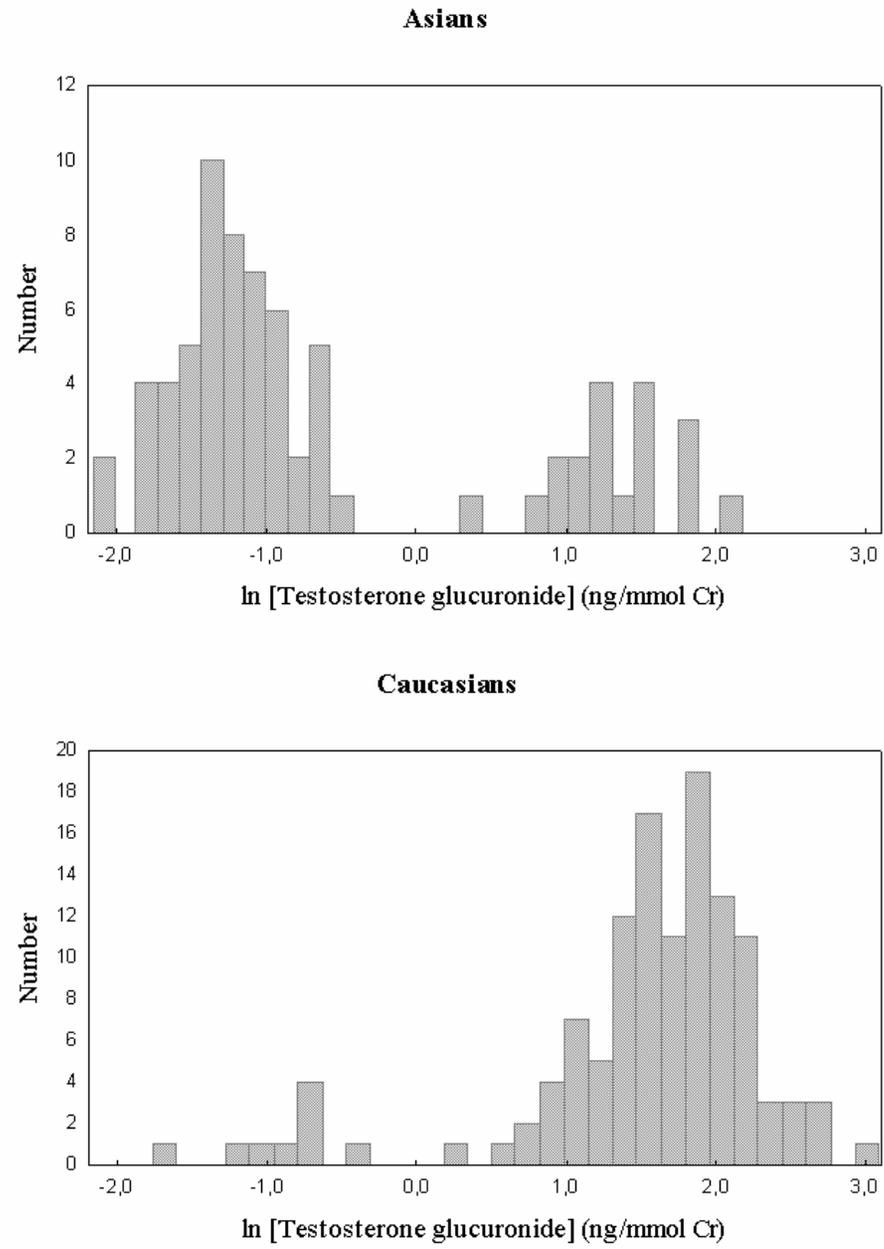


Figure 1b)

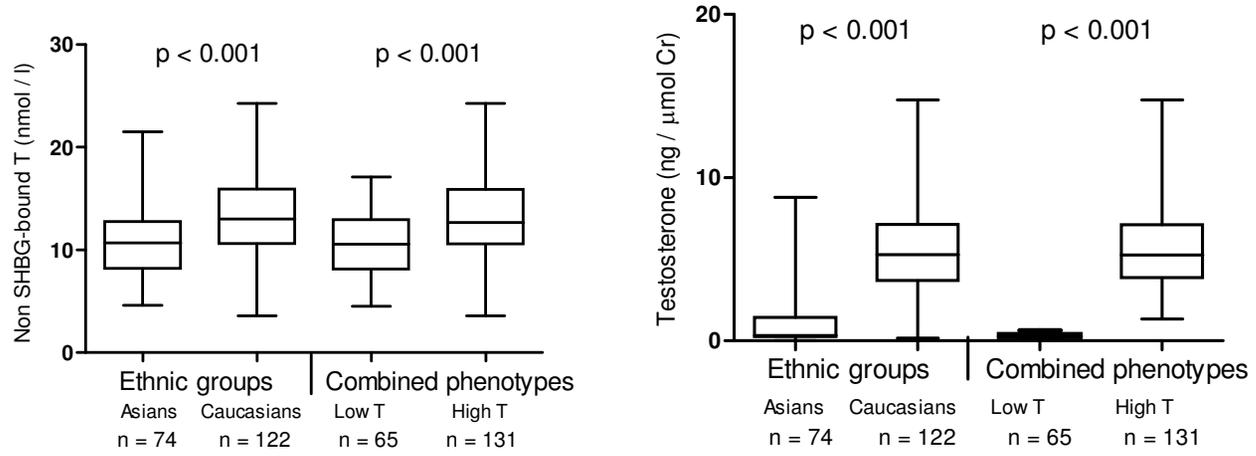


Figure 2)

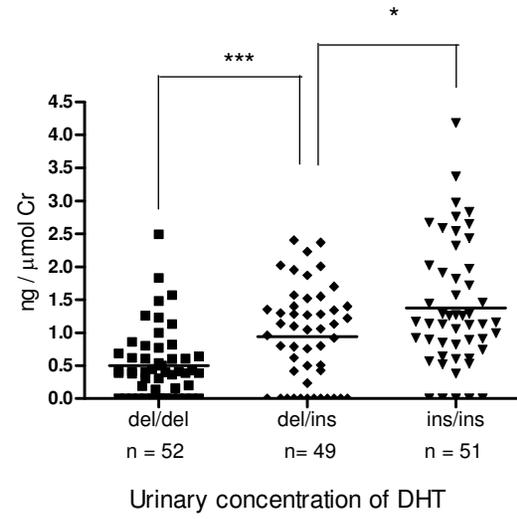
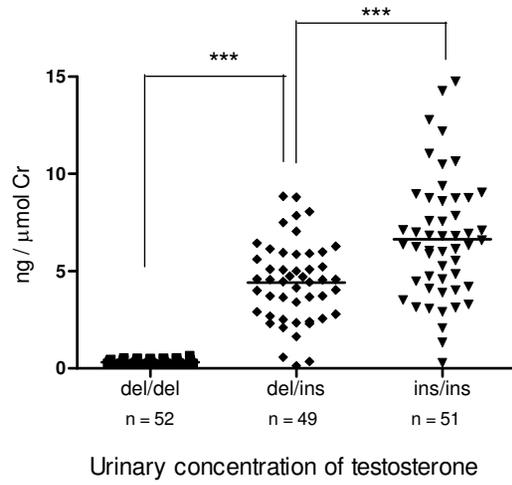


Figure 3)

