Lena Ekström, Jenny Jakobsson, Mats Garle, and Anders Rane

Large differences in testosterone excretion in Korean and Swedish men are strongly associated with a UDP-glucuronosyl transferase 2B17 polymorphism

Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska University Hospital, SE-141 86 Stockholm, Sweden;

Abstract: The objective of the study was to evaluate the contribution of the UGT2B17 deletion polymorphism to the interethnic variation of testosterone/epitestosterone ratio. Urine from 122 Swedish and 74 Korean healthy men was analyzed for testosterone and epitestosterone glucuronides. 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 homozygous for the UGT2B17 deletion genotype had no or negligible amounts of urinary testosterone. The deletion/deletion genotype was seven times more common in the Korean (66.7%) than the Swedish population (9.3%). These data are of great importance for the anti-doping test programs.

Introduction: It has been established that Oriental people generally have lower testosterone/epitestosterone (T/EpiT) values (<0.5) than Caucasians that often have values around 1. The limited effect of androgen doping on testosterone excretion in Asian populations increases the risk of false-negative results. Testosterone is excreted mainly as glucuronide conjugates [1] after glucuronidation by uridine diphospho (UDP)-glucuronosyl transferases (UGT). These enzymes have a key role in the homeostasis of a number of endogenous molecules including steroid hormones [2], and they facilitate their excretion in bile and urine. There are seven members of the UGT2B subfamily. One of these, UGT2B17, was found to be particularly active in androgen glucuronidation [3]. It was recently described that some individuals lack the UGT2B17 gene [4]. The physiological consequences of this gene deletion polymorphism are unknown.

Given this background, we decided to study the urinary excretion pattern of testosterone and other androgens in relation to the UGT2B17 deletion polymorphism in nonathlete volunteers of Caucasian and Asian ethnic descent.

Methods*:* Seventy-four unrelated Korean male subjects aged 21–39 yr (mean 26.3 ± 3.5 yr) and the 122 Caucasian men aged 18.0–20.1 yr (mean 18.9 ± 0.6 yr) were included. The populations have previously been described [5]. Spot urine samples were collected and immediately frozen at –20 C. To minimize any influence of diurnal variation, all blood and urine samples were collected between 2 and 7.30 p.m. Urinary unconjugated steroids (typically < 1% of glucuronide fraction) + steroid glucuronides were determined by gas chromatography-mass spectrometry after hydrolysis of the conjugates with ß-glucuronidase as described [6] with minor modifications [7]. The between-subject variability in urine dilution was corrected for by dividing the concentration values by the urinary creatinine (Cr) concentration. Genotyping of UGT2B17 deletion polymorphism was performed as previously described [5]. The number of subjects with DNA samples available for genotyping was 66 Koreans and 86 Swedes.

Results and Discussion: The median T/EpiT value in the Swedish population was 1.7 whereas the median value in the Koreans was 0.15 (fig 1). The distribution of the natural logarithms of urinary testosterone/Cr concentrations showed a distinct bimodal pattern in both the Korean and Swedish population (Fig 2). 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 median value of testosterone excretion was 16 times higher in the Swedish population [5.4 (3.7–7.1) ng/μmol Cr] than the Korean population [0.33 (0.25–0.58) ng/μmol Cr]. There were no differences between the ethnic groups in Cr excretion.

We have shown that individuals absent of the UGT2B17 gene (deletion) all belong to the low T/EpiT-ratio group (below 0.4) (fig 3). All of the Koreans and Swedes with the del/del genotype (homozygous for the deletion allele) had no or negligible amounts of urinary testosterone (fig 3). Three of the Asian subjects with one (del/ins) or two copies (ins/ins) of the UGT2B17 gene 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. The epitestosterone concentrations in urine did not differ between the genotype groups.

In conclusion, 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 genetic subgroups according to their urinary testosterone levels. We have also identified the genotype underlying this phenotypic pattern. We have shown that individuals absent of the UGT2B17 gene all belong to the low testosterone group. Absence of the UGT2B17 gene was seven times more common in the Korean than the Swedish population sample.

A direct consequence of this is that the commonly used testosterone to epitestosterone ratio, used to detect testosterone abuse, would be more useful if taking the genetic constitution into account. We are now investigating how the T/EpiT pattern, differ between the genotype groups after testosterone administration in healthy volunteers. Depending of the outcome it is possible that the T/EpiT ratio may be complemented with a genotyping assay in the future to improve the sensitivity and specificity of the test program.

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Figures:

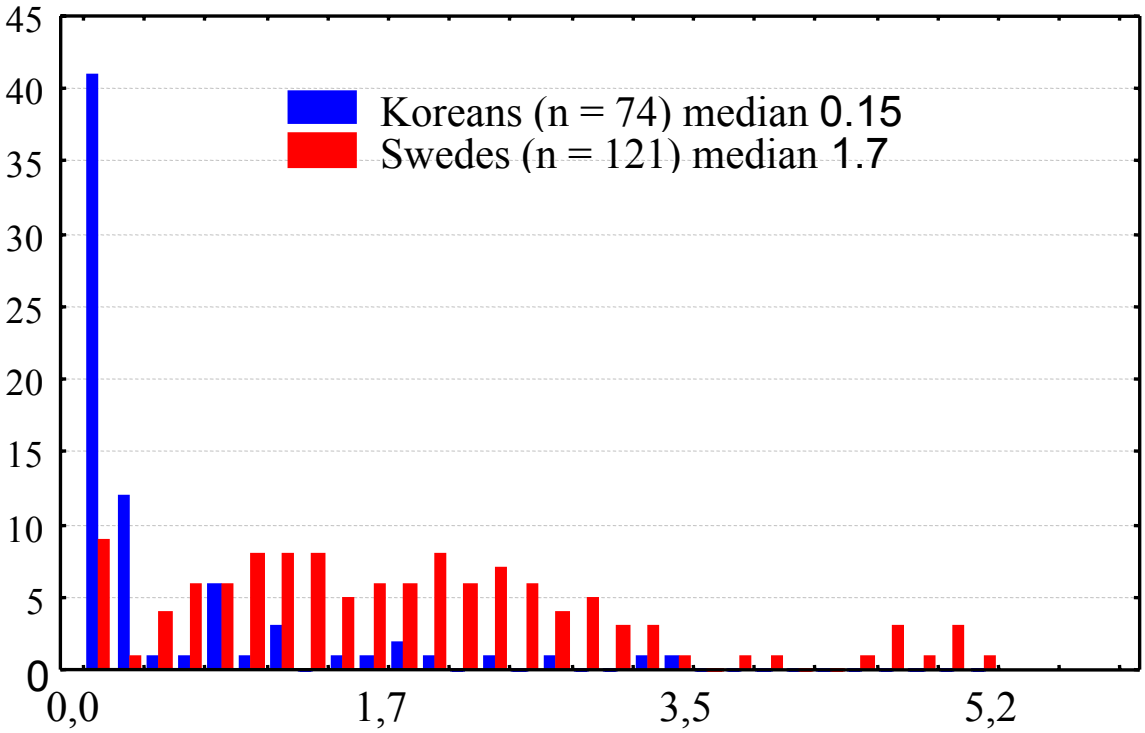

Figure 1. *Frequency distribution of urinary T/EpiT-value in Swedish and Korean subjects. The median T/EpiT-value was 0.15 and 1.7 in the Korean and the Swedish population, respectively.*

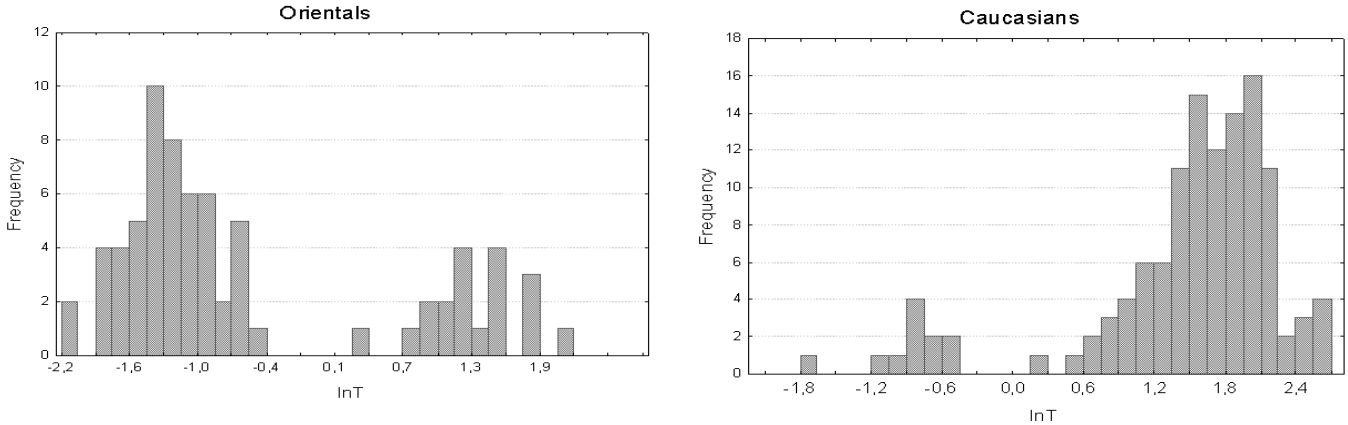

Figure 2 *Frequency distribution of natural logarithms of urinary unconjugated + glucuronide conjugated testosterone (nanograms per micromole Cr) in a Korean (n = 74) (left panel) and Swedish (n = 122) (right panel) population of healthy men.*

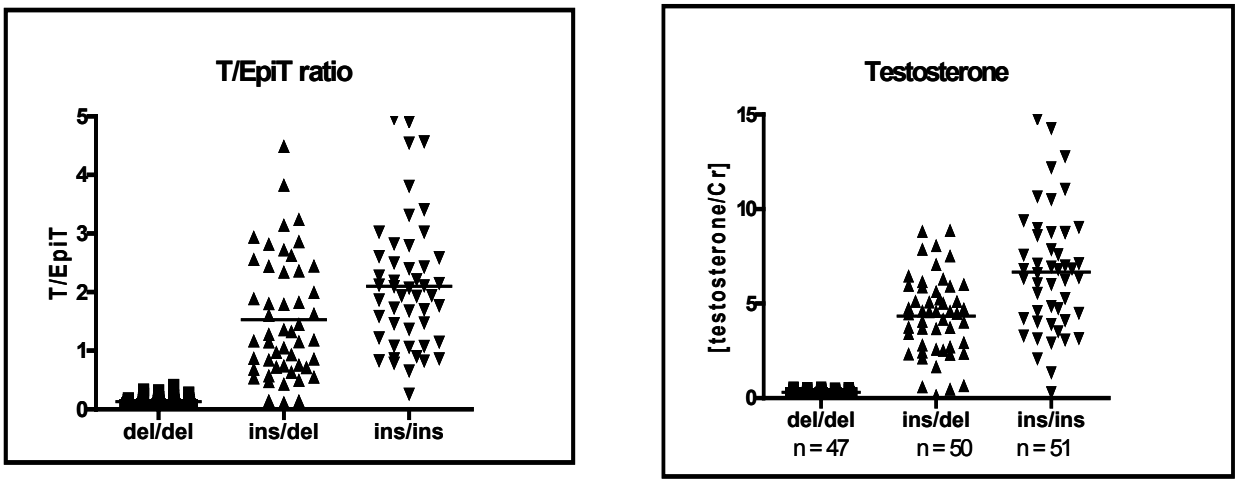

Figure 3 *Relation between T/EpiT-ratio (left panel) and urinary unconjugated + glucuronide conjugated testosterone glucuronide (nanograms per micromole Cr) (right panel) and UGT2B17 genotype in the combined Swedish and Korean population samples. Del=deletion of the UGT2B17 gene, ins=insertion of the 2B17 gene*

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