

A Common Deletion in the Uridine Diphosphate Glucuronyltransferase (*UGT*) *2B17* Gene Is a Strong Determinant of Androgen Excretion in Healthy Pubertal Boys

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Background: Testosterone (T) is excreted in urine as water-soluble glucuronidated and sulfated conjugates. The ability to glucuronidate T and other steroids depends on a number of different glucuronidases (UGT) of which *UGT2B17* is essential. The aim of the study was to evaluate the influence of *UGT2B17* genotypes on urinary excretion of androgen metabolites in pubertal boys.

Study Design: A clinical study of 116 healthy boys aged 8–19 yr. *UGT2B17* genotyping was performed using quantitative PCR. Serum FSH, LH, T, estradiol (E2), and SHBG were analyzed by immunoassays, and urinary levels of androgen metabolites were quantitated by gas chromatography/mass spectrometry in all subjects.

Results: Ten of 116 subjects (9%) presented with a homozygote deletion of the *UGT2B17* gene (del/del), whereas 52 and 54 boys were hetero- and homozygous carriers of the *UGT2B17* gene (del/ins and ins/ins), respectively. None of the reproductive hormones were affected by *UGT2B17* genotype. In all subjects, mean urinary T/epitestosterone ratio was 1.56 [1.14 (sd); 0.1–6.9 (range)] and unaffected by age or pubertal stage. Subjects with homozygous deletions of *UGT2B17* had significantly lower urinary levels of T and 5 α - and 5 β -androstenediol. Mean urinary T/epitestosterone was significantly reduced in del/del subjects [0.29 (0.30); 0.1–1.0 (range), $P < 0.0001$].

Conclusion: In pubertal boys, a common homozygous deletion in the *UGT2B17* gene strongly affected urinary excretion pattern of androgen metabolites but did not influence circulating androgen levels. (*J Clin Endocrinol Metab* 94: 1005–1011, 2009)

In male puberty, the hypothalamic-pituitary-gonadal axis is reactivated by hitherto unknown stimuli (1, 2). This reactivation results in increasing secretion of testosterone (T), which is produced in the testicular Leydig cells after stimulation of LH. The endogenous T virilizes external genitals and increases muscle and bone mass in prepubertal boys until the age of approximately 25 yr where peak bone mass is obtained. T is produced throughout adult life with an annual decline of approximately 1–2% (3) and is important for energy, libido, and muscle and bone function.

T exerts its effects through binding to the androgen receptor (AR) that is present in numerous androgen-sensitive tissues and

organs. Transcriptional activity of AR after activation by T may vary and depends on the T concentration as well as on the number of CAG repeats in the AR gene (4). Furthermore, the biological activity of circulating T depends on other factors such as binding to SHBG and conversion of T to estradiol (E2) by aromatization as well as conversion to dihydrotestosterone (DHT) by 5 α -reductase. Finally, the biological activity of T is dependent on its metabolism and rate of excretion, but few studies have evaluated the influence of T metabolism on the onset and progression of puberty.

Testosterone is excreted in urine as water-soluble glucuronidated and sulfated conjugates. The ability to glucuronidate

T and other steroids depends on a number of different glucuronidases [uridine diphospho-glucuronyltransferases (UGT)]. Two groups of UGT proteins exist depending on their primary protein structure: UGT1 and UGT2 (UGT2A and UGT2B). Especially, UGT2B enzymes (UGT2B4, -B7, -B10, -B11, -B15, and -B17) are important for T excretion and are encoded for by genes that are clustered on chromosome 4 (4q13–21.1) (for review see Ref. 5). A common homozygote deletion (del/del) of the gene that encodes UGT2B17 is present in approximately 10% of Caucasians and much more frequently in Asians (approximately 67%) (6). Deletion of *UGT2B17* exerts influence on the glucuronidation of T, and thereby changes urinary levels of T and several T metabolites, and has also been related to fat mass and insulin sensitivity in healthy men (7). Recently, subjects with homozygous deletions of *UGT2B17* showed markedly reduced T/epitestosterone (E) urinary ratios after exogenous androgen administration (8), which prompted our interest in this area.

We hypothesize that the common genetic variations in the gene encoding *UGT2B17* could influence androgen excretion and thereby the endogenous androgen homeostasis in puberty.

We therefore investigated the influence of the *UGT2B17* genotype on serum testosterone levels and urinary excretion pattern of T and its metabolites in healthy pubertal boys.

Subjects and Methods

Subjects

All participants were recruited as a part of the Copenhagen Puberty Study from three primary schools in the Copenhagen Community. One hundred sixteen healthy Caucasian children and adolescents aged 8–19 yr volunteered. No previous or present medical history of ongoing conditions was reported. No medications were reported taken.

Pubertal development

Pubertal development was described according to the classification by Tanner (9, 10). Boys were classified by genital (G1-5) and pubic hair (PH1-6) stages. In addition, testicular volumes were estimated using a Prader orchidometer (11).

Analyses

Serum T was determined by RIA (Siemens Medical Solutions Diagnostics, Ballerup, Denmark). The detection limit was 0.23 nmol/liter, and intra- and interassay coefficients of variation (CV) were less than 10%. Serum FSH and LH were measured by time-resolved immunofluorometric assays (Delfia; PerkinElmer, Boston, MA) with detection limits of 0.06 and 0.05 IU/liter for FSH and LH, respectively. Intra- and interassay CV were less than 5% in both gonadotropin assays. SHBG was determined by a time-resolved immunofluorescence assay (Delfia; Wallace Oy, Turku, Finland) with a detection limit of 0.23 nmol/liter. Intra- and interassay CV were 5.8 and 6.4%, respectively. Estradiol was measured by RIA [Pantex, Santa Monica, CA (before 1998 distributed by Immuno Diagnostic Systems, Boldon, UK)]. The detection limit was 18 pmol/liter, and the intra- and interassay CV were less than 8 and 13%, respectively (12).

UGT2B17 deletion polymorphism

DNA was isolated from leukocytes from peripheral blood using the QuickGene-810 Nucleic Acid Isolation System (Fujifilm, Life Science

Products, Tokyo, Japan), with the QuickGene DNA whole blood kit and QIAamp 96 DNA Blood Kit (12) (QIAGEN, Valencia, CA). The concentration and quality were measured using a NanoDrop ND-1000 Spectrophotometer (Saveen Werner AB, Malmö, Sweden). The gene copy number analysis of *UGT2B17* using the quantitative PCR technique was performed on the Mx3000P platform from Stratagene (Cedar Creek, TX); the general protocol is described in detail elsewhere (13). Primers for measurements of the gene dosage of *UGT2B17* (mapped to exon 1) and *GAPDH* resulted in product sizes of 106 and 78 bp, respectively, verified by gel electrophoresis. Primer sequences are available in the public RTPrimerDB database (<http://medgen.Ugent.be/rtprimerdb/>) (gene (RTPrimerDB-ID): *UGT2B17* (10318) (14). Primer sequences were forward (Fw) 5'-GCT CTG GGA GTT GTG GAA AG-3' and reverse (Rev) 5'-ATC ACC TCA TGA CCC CTC TG-3' (DNA Technology A/S, Århus, Denmark). For normalization primers for the *GAPDH* gene (Fw 5'-CTC CCC ACA CAC ATG CAC TTA-3' and Rev 5'-TTG CCA AGT TGC CTG TCC TT-3') were used for analysis of the same patient, and for quantification, the ratio was calibrated to a normal male reference control (for details see Refs. 13 and 15). In short, mixtures of Fw and Rev primers were denatured for 3 min at 95 C and incubated on ice until use. Reaction tubes contained DNA in the range of 4–21 ng, 15 μ l Brilliant SYBR Green QPCR Master Mix (Stratagene), 7.0 μ l primer mixture of *UGT2B17* (final concentration Fw and Rev 300 nM) or *GAPDH* (final concentration Fw and Rev 100 nM). Conditions for amplification were as follows: one cycle at 95 C for 10 min; 40 cycles at 95 C for 30 sec, 62 C for 1 min, and 72 C for 1 min; and one cycle at 95 C for 1 min, 62 C for 1 min, and 95 C for 30 sec (the last cycle for producing a dissociation curve). For statistical analysis of data, mean ratios, SD, variance, 95% confidence intervals, and reference ranges of mean ratio \pm 2 SD were calculated.

Urinary T/E ratio

A morning urinary sample was collected in all boys. Time for last urinary voiding before collection, urinary volume, and time at collection were recorded. Urinary samples were stored at -20 C until analysis.

Urine analysis

The sample preparation applied for the determination of endogenous steroids followed with certain modifications the procedure for the identification of anabolic-androgenic steroids used in doping control laboratories (16). To 2.5 or 5 ml urine, depending on the specific gravity of the urine sample, a mixture of internal standards was added. The mixture consisted of D₃-T, D₃-E, D₃-5 α -androstane-3 α ,17 β -diol, D₅-5 β -androstane-3 α ,17 β -diol, D₄-androsterone, D₅-ethiocholanolone, D₃-5 α -DHT glucuronide (National Measurement Institute, NMI, Sydney, Australia), and methyltestosterone (Sigma-Aldrich, Oslo, Norway). After adding a sodium acetate buffer (pH \sim 5) the samples were subjected to solid-phase extraction with Bond-Elute C-18, 200 mg (Varian, Palo Alto, CA). The eluate was evaporated under a stream of nitrogen and redissolved in 100 μ l methanol and 1 ml phosphate buffer (pH 6.5–7). The glucuronidated steroids were hydrolyzed at 50–55 C for 1 h with β -glucuronidase from *Escherichia coli* (Roche Diagnostics, Mannheim, Germany). The hydrolyzed sample was extracted with 5 ml *tert*-butyl methyl ether after adding tris(hydroxymethyl)aminomethane buffer (Merck, Darmstadt, Germany) (pH 9.5–9.8) while shaking for 10 min at room temperature. After centrifugation, the organic phase was evaporated and the samples were derivatized with *N*-methyl-*N*-trimethylsilyltrifluoroacetamid (MSTFA) (Macherey-Nagel, Düren, Germany), ammonium iodide, and ethane-thiol (1000:2:6; vol/wt/vol) to their enol-trimethylsilyl ether derivatives. All chemicals and solvents used were of analytical or HPLC grade. The analysis of the urinary steroids was performed with gas chromatography/mass spectrometry using an Agilent 5973 GC-MS (Agilent, Santa Clara, CA). The instrument was operated in single-ion monitoring mode. The quantitative analysis was performed with an isotope dilution mass spectrometry method using a five-point calibration curve with a mixture of

selected endogenous steroids prepared in artificial urine (Cerilliant, Round Rock, TX). The mixture contained the following steroids: T, E, androsterone, etiocholanolone (Sigma-Aldrich, Oslo, Norway), 5 α -androstane-3 α ,17 β -diol, 5 β -androstane-3 α ,17 β -diol, and 5 α -DHT (Steraloids, Newport, RI). A quality control sample was prepared and analyzed together with the calibration samples for every batch of samples. The intermediate precision of the assay was less than 9% for the steroids analyzed. The urinary steroid concentrations constitute the free (generally much less than 5% of the total) plus the glucuronide fraction. To account for the considerable variability in urine dilution, the concentra-

tions are corrected to a specific gravity of 1.020 (17). Illustration of the relevant steroid metabolites and their association to each other are shown in Fig. 1.

Statistical methods

Data are presented as mean, SD, and ranges, and all circulating and urinary hormones were compared between groups by ANOVA with UGT2B17 genotype and age as independent variables *vs.* the dependent variables.

Ethics

The study was in accordance with the ethical principles of the Helsinki II declaration. The study protocol was approved by the local ethics committee (Ref. no. KF 01 282214 and KF 11 2006-2033). All children and parents gave their informed written consent.

Results

Baseline characteristics and serum hormone levels of the subjects according to pubertal stage are shown in Table 1.

Ten of 116 subjects (9%) presented with a homozygous deletion of the *UGT2B17* gene (del/del), whereas 52 and 54 boys were hetero- and homozygous carriers of the *UGT2B17* gene (del/ins and ins/ins), respectively. Serum levels of FSH, LH, T, E2, and the T/LH ratio significantly increased with age as well as with pubertal stages, whereas SHBG levels declined with increasing age or pubertal stages. None these circulating hormones were affected by *UGT2B17* genotype in ANOVA controlling for age (Fig. 2 and Table 2).

Urinary steroid levels according to age and *UGT2B17* genotype are shown in Fig. 3. Urinary T excretion significantly increased with increasing age and pubertal stage (both $P < 0.0001$) and significantly correlated with serum T ($P < 0.0001$). Urinary E increased significantly with increasing age and pubertal stage (both $P < 0.001$). In all subjects, mean urinary T/E ratio was 1.56 [1.14 (SD); 0.1–6.9 (range)] and unaffected by age or pubertal stage. Two midpubertal (genital stages 3 and 4) subjects (both 12 yr of age) had T/E ratios above 4 (5.5 and 6.9, respectively).

Urinary steroid metabolites are shown according to *UGT2B17* genotype in Table 2 and Fig. 3. *UGT2B17* genotype significantly affected urinary levels of T and 5 β -androstenediol (Bdiol) even after adjustment for age. Urinary 5 α -androstenediol (Adiol) levels were lower in del/del subjects although to a lesser degree ($P = 0.043$). Urinary androsterone and etiocholanolone levels were not affected by *UGT2B17* genotype. Thus, urinary T/E was significantly reduced in del/del subjects (Fig. 3), whereas urinary ratios of androsterone/T and androsterone/etiocholanolone were unaffected by *UGT2B17* genotype. By contrast, urinary ratio of Adiol to Bdiol was significantly increased in del/del subjects (Fig. 3).

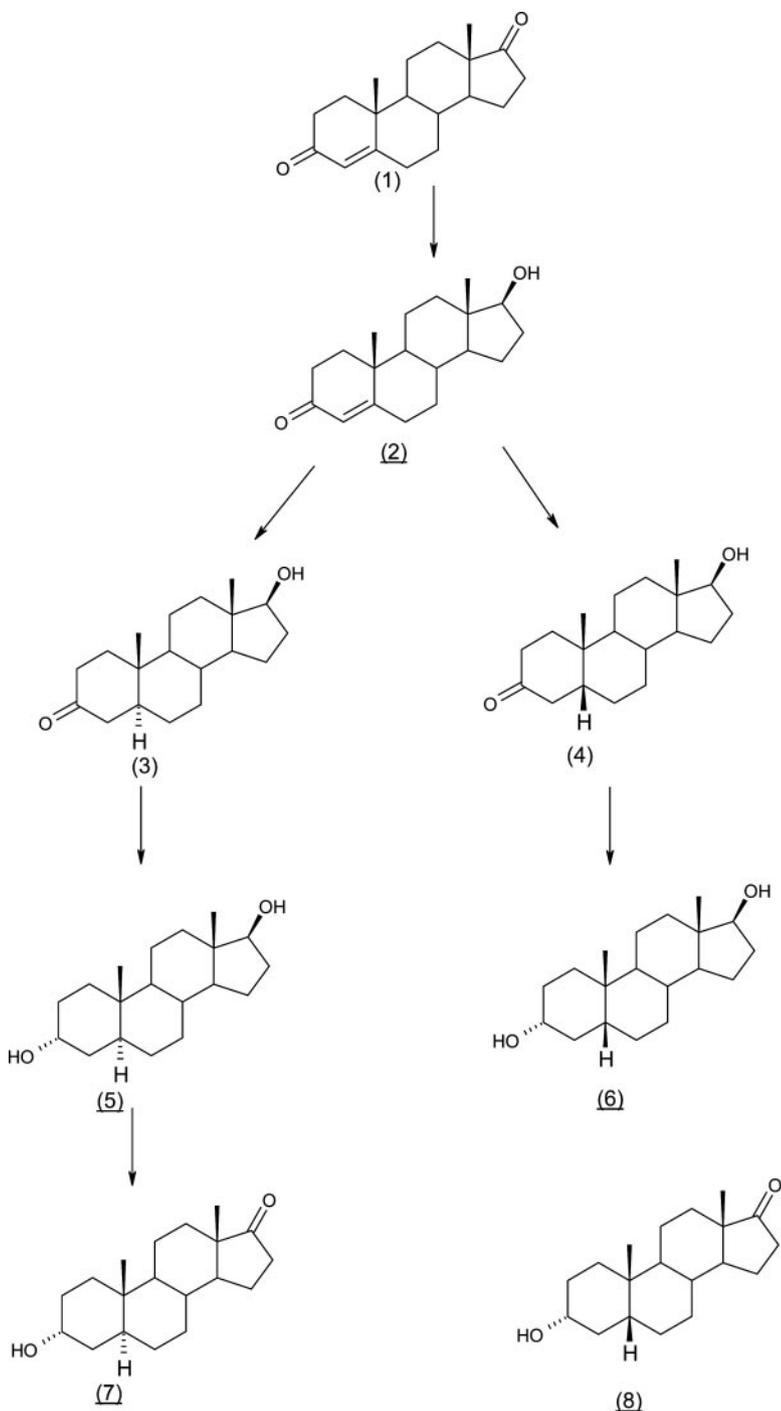


FIG. 1. Metabolism of T: 1) 4-androstenedione, 2) T, 3) 5 α -DHT, 4) 5 β -DHT, 5) 5 α -androstane-3 α ,17 β -diol, 6) 5 β -androstane-3 α ,17 β -diol, 7) androsterone, and 8) etiocholanolone. Steroids analyzed in this study are underlined. E, which is a 17 α -hydroxy epimer of T, undergoes similar metabolism and is converted to the respective 3 α ,17 α -diols (34).

TABLE 1. Auxological and hormonal characteristics in 116 healthy boys and adolescents according to pubertal stage

	Genital stage				
	1	2	3	4	5
n	28	22	5	8	62
Age (yr)	10.5 ± 1.0	12.4 ± 1.1	12.5 ± 0.5	13.8 ± 1.2	17.0 ± 1.6
Height (cm)	144.1 ± 6.1	155.4 ± 7.5	162.1 ± 2.9	168.7 ± 5.2	180.1 ± 8.2
Height (SDS)	0.36 ± 0.83	0.43 ± 1.29	1.10 ± 0.75	0.70 ± 0.79	0.37 ± 1.16
Weight (kg)	36.4 ± 5.0	44.5 ± 8.6	49.8 ± 4.6	57.3 ± 11.3	69.2 ± 10.2
BMI (kg/m ²)	17.5 ± 2.1	18.3 ± 2.4	19.0 ± 1.8	20.1 ± 3.3	21.3 ± 2.5
BMI (SDS)	0.28 ± 1.29	0.22 ± 1.34	0.53 ± 0.87	0.64 ± 1.64	0.26 ± 1.33
T (nmol/liter)	0.03 ± 0.11	2.0 ± 2.4	3.7 ± 4.2	11.3 ± 4.7	16.0 ± 5.3
SHBG (nmol/liter)	116 ± 39	117 ± 35	59 ± 12	66 ± 16	39 ± 15
E2 (pmol/liter)	6.6 ± 6.3	11.0 ± 10.5	15.2 ± 26.0	14.8 ± 13.2	43.4 ± 18.5
FSH (IU/liter)	1.2 ± 0.8	2.2 ± 1.0	1.6 ± 0.9	4.6 ± 3.1	3.5 ± 1.8
LH (IU/liter)	0.3 ± 0.5	1.2 ± 0.6	1.4 ± 0.7	2.5 ± 0.8	3.0 ± 1.2

Results are presented as mean ± sd. BMI, Body mass index; SDS, sd score.

Discussion

In our detailed study of 116 healthy Caucasian boys and adolescents, we found that the presence of a common homozygous deletion in the *UGT2B17* gene strongly affected urinary androgen excretion but not circulating androgen levels. To our knowledge, this has not been reported previously in adolescents.

We found that 10 of 116 subjects (9%) presented with a homozygous deletion of the *UGT2B17* gene (del/del), and 52 and 54 boys were hetero- and homozygous carriers of the

UGT2B17 gene (del/ins and ins/ins), respectively. This prevalence of *UGT2B17* polymorphism is in accordance with other studies of Caucasian subjects (6, 18), whereas Asians have a much higher prevalence (67%) of the homozygous deletion of *UGT2B17* (6).

There is a marked variability in the timing and progression of human puberty (for review see Ref. 2). Timing of puberty follows a familial pattern and therefore seems to be controlled by strong genetic factors (19). The variability in timing and progression of puberty is considered to be controlled by multiple genes that are

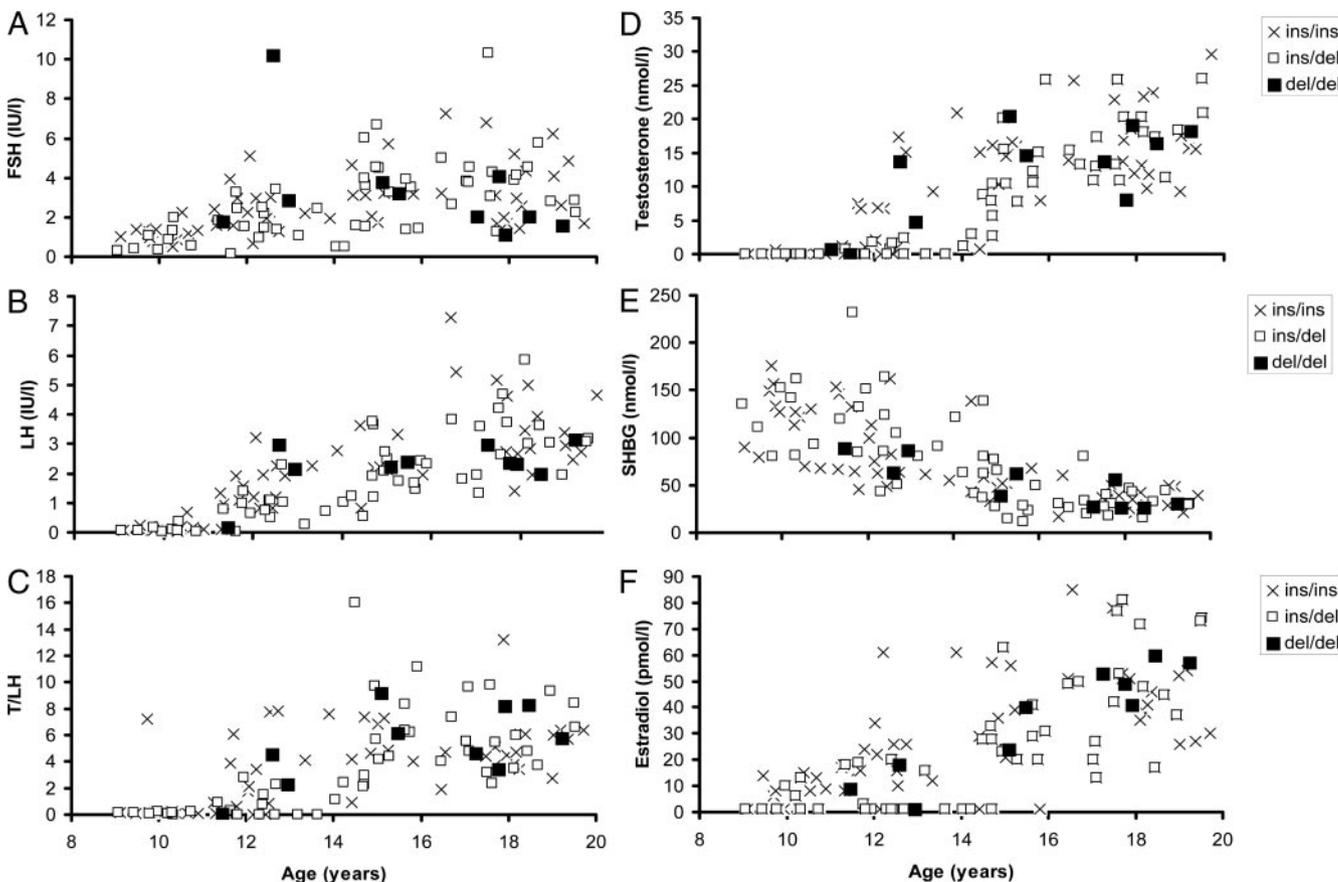


FIG. 2. Serum FSH (A), LH (B), T/LH (C), T (D), E2 (E), and SHBG (F) in healthy boys and adolescents according to chronological age and *UGT2B17* genotype: x, ins/ins; □, ins/del; ■, del/del.

TABLE 2. Urinary levels of androgen metabolites and their ratios in relation to *UGT2B17* gene copy number in 116 healthy boys and adolescents

	<i>UGT2B17</i> gene copy number			<i>P</i> value
	0	1	2	
No. (%)	10 ± 8.6	52 ± 44.8	54 ± 46.6	
Age (yr)	15.8 ± 2.7	14.4 ± 2.9	14.0 ± 3.1	NS
Dependent variable				
T (ng/ml)	6.2 ± 7.9 (2.0–27.1)	22.7 ± 23.4 (1.0–96.9)	29.6 ± 27.4 (1.0–141)	<0.0001
E (ng/ml)	26.6 ± 25.2 (1.48–86.4)	23.3 ± 23.6 (0.8–77.8)	19.6 ± 23.1 (0.7–84.5)	NS
Androsterone (ng/ml)	2410 ± 952 (460–3532)	1966 ± 1333 (286–5131)	1886 ± 1869 (117–8447)	NS
Etiocholanolone (ng/ml)	1202 ± 586 (366–2173)	1067 ± 663 (152–3405)	1186 ± 1317 (107–7708)	NS
Adiol (ng/ml)	39 ± 20 (10–71)	49 ± 34 (12–151)	47 ± 36 (9–151)	0.043
Bdiol (ng/ml)	24 ± 12 (10–49)	75 ± 51 (18–212)	106 ± 114 (11–546)	<0.0001
T/E	0.29 ± 0.30 (0.1–1.0)	1.38 ± 0.81 (0.3–3.9)	2.08 ± 1.15 (0.1–7.0)	<0.0001
Andro/T	713 ± 88 (88–1401)	188 ± 166 (32–786)	123 ± 103 (29–571)	<0.0001
Andro/Etio	2.6 ± 2.0 (0.3–7.7)	1.9 ± 0.7 (0.6–3.6)	1.9 ± 1.0 (0.3–7.7)	NS
Andro/Bdiol	1.6 ± 0.5 (1.0–2.4)	0.7 ± 0.3 (0.2–1.6)	0.7 ± 0.3 (0.2–1.6)	<0.0001

Values are presented as mean ± SD (range). *P* values are from ANOVA with *UGT2B17* genotype and age as independent variables vs. the dependent variables. Andro, Androsterone; Etio, etiocholanolone; NS, not significant.

yet to be identified. Null mutations in selected genes like *GPR54*, the receptor for kisspeptin, may cause a complete absence of puberty (20), and recently, an activating mutation in *GPR54* was identified in a girl with central precocious puberty (21). However, little is known about genetic polymorphisms that influence pubertal timing within the normal range. In this context, we consider the common deletion of the *UGT2B17* gene potentially interesting. We found that the *UGT2B17* deletion strongly influenced the urinary excretion pattern of androgens in healthy pubertal boys and hypothesized that this genetically determined variability of androgen metabolite excretion could influence the endogenous circulating sex steroid levels. However, we found no differences in plasma levels of reproductive hormones according to *UGT2B17* genotype. If androgens are cleared at a much slower rate in *UGT2B17*-deleted subjects (because they fail to glucuronidate T), less T production is potentially needed in these subjects to maintain adequate T levels. Nevertheless, we did not find evidence of lowered LH drive on the Leydig cells as evaluated by the T/LH ratio.

The almost constant ratio between urinary T glucuronide and E glucuronide levels is monitored in doping control analysis to get indications for T abuse. E is the 17 α -epimer of T and has no known physiological function. Initially, an upper normal limit for the T/E ratio in healthy subjects was 6 (for review see Ref. 22). However, since 2005, World Anti-Doping Agency changed the reporting threshold for T/E from 6 to 4 to improve the sensitivity for the detection of T abuse. In our present study, mean urinary T/E was 1.56, which is in accordance with other studies of Caucasian adults. However, two subjects had T/E ratios above the World Anti-Doping Agency threshold of 4 (5.5 and 6.9, respectively). This is in line with another study in which two of 141 adolescents had a T/E ratio above 6 (23). In this study, the authors concluded that marked increases in T/E can be observed as a normal physiological phenomenon in midpuberty (24) in line with others (25). The appearance of naturally elevated T/E ratios (26) has made it mandatory to follow up an atypical finding (T/E >4) by additional investigations (e.g. isotope ratio mass spectrometry) (27). In our present study, we found that urinary

T/E ratio was unaffected by age and pubertal stage in accordance with Dehennin and co-workers (28) who studied 140 sporting male adolescents. Thus, some controversy exists.

We found a significantly reduced urinary T/E ratio in boys who lack the *UGT2B17* gene (del/del). The lowered T/E ratio in del/del subjects was caused by lowered urinary T excretion, because urinary E seemed unaffected by the genotype. Whereas T is a known substrate for the *UGT2B17* gene product, little is known about glucuronidation of E (for review see Ref. 5). The fact that glucuronidated T can be detected in del/del subjects even though at low levels suggests that other glucuronidases must be able to glucuronidate T. Thus, *UGT2B15* may glucuronidate T to some extent and was found to be up-regulated in the absence of the *UGT2B17* gene (29). We also found significantly lowered urinary excretion of the T metabolites Adiol and Bdiol. Interestingly, we found that Bdiol was markedly reduced as opposed to Adiol, which was only marginally, although statistically significantly, reduced in *UGT2B17* del/del subjects. This resulted in a significantly increased ratio between the Adiol and Bdiol in del/del subjects. Together with other indicators, a ratio between Adiol and Bdiol of more than 1.5 in men is considered suspicious of DHT abuse and should be followed up by further investigations (16). We found that seven subjects had an Adiol/Bdiol ratio above 1.5. We have no explanation for the apparent preferential glucuronidation of Bdiol by the *UGT2B17* enzyme. Surprisingly, there was no effect of genotype on androsterone and etiocholanolone excretion. On the other hand, these oxidized end products from Adiol and Bdiol, respectively, may also derive from E, which could explain the lack of effect on androsterone and etiocholanolone by *UGT2B17* deletions.

Hypothetically, subjects with homozygous *UGT2B17* deletions could excrete T through other phase II metabolites such as T sulfated conjugates. However, Borts and Bowers reported that subjects with low urinary excretion of T did not produce larger than normal amounts of T sulfate (30).

Recently, an interesting paper clearly demonstrated the importance of the *UGT2B17* deletion on T/E urinary excretion after an im injection of T enanthate in 55 healthy men who were

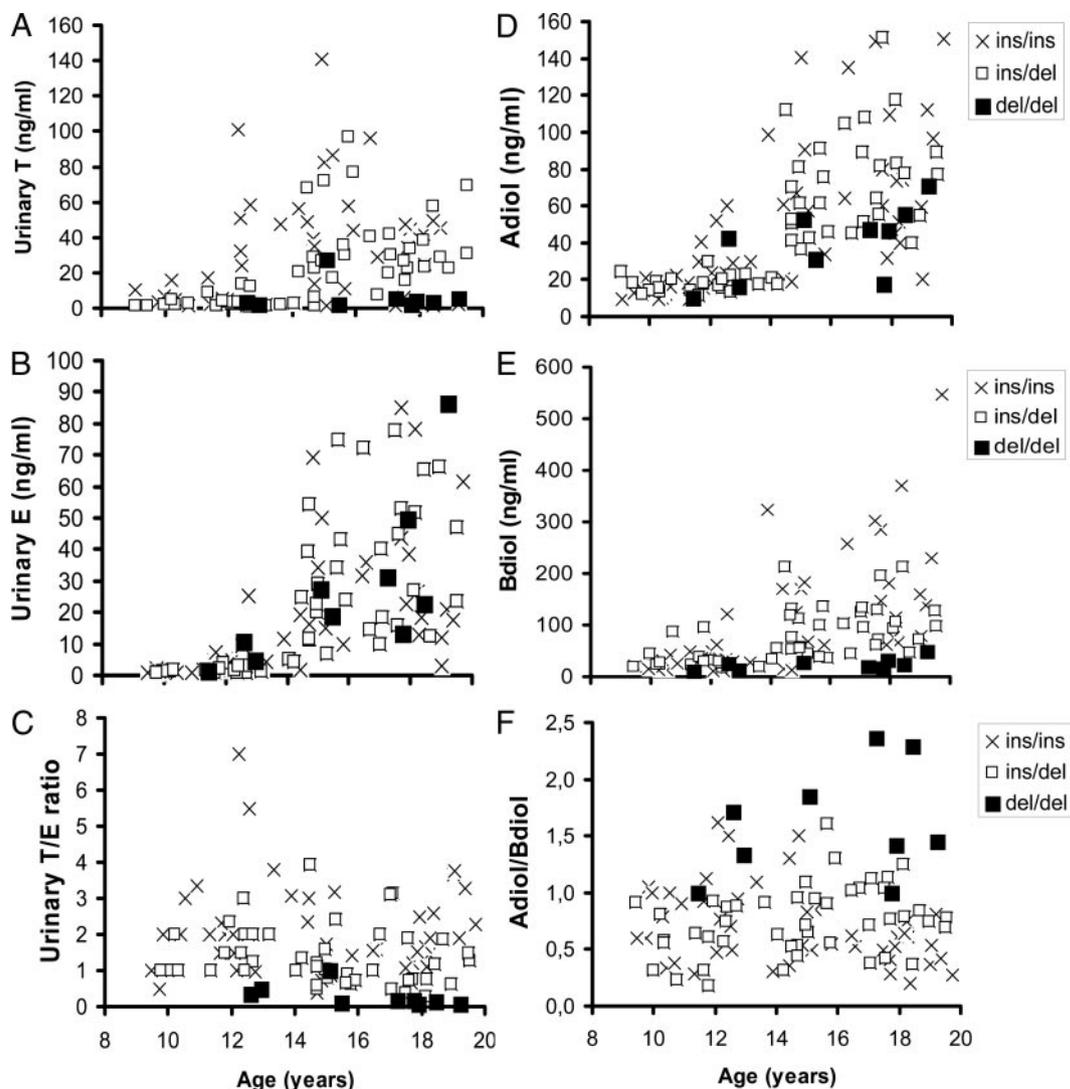


FIG. 3. Urinary T (A), E (B), T/E ratio (C), Adiol (D), Bdiol (E), and Adiol/Bdiol ratio (F) in healthy boys and adolescents according to chronological age and *UGT2B17* genotype: ×, ins/ins; □, ins/del; ■, del/del.

selected on the basis of their *UGT2B17* genotype (8). They found that the degree and rate of increase in glucuronidated T was 20-fold lower in subjects with a homozygous *UGT2B17* deletion after T administration and that 40% of the del/del subjects never reached a urinary T/E ratio above 4 after T injection.

Altogether, it can be suggested that T abuse in subjects with homozygous deletions of the *UGT2B17* gene is less likely to be detected by conventional urinary screening. Conversely, DHT abuse may be more readily detected in such del/del individuals compared with subjects who carry one or two copies of the *UGT2B17* gene due to an increased ratio of Adiol/Bdiol.

We found no effect of *UGT2B17* genotype on serum levels of T in our adolescent boys. Likewise, Swanson *et al.* (7) did not find any effect of *UGT2B17* genotype on serum T or DHT in healthy adult men. One would have anticipated that subjects devoid of the *UGT2B17* gene (and hereby not being able to excrete glucuronidated T in the urine) might have increased serum levels of T, but this is apparently not the case. In fact, Korean men have lower serum T levels compared with Caucasian men despite the fact that the *UGT2B17* deletion is very common among Korean

men (6). We also did not find evidence of altered Leydig cell activity (determined as sensitivity to LH) in our del/del subjects, because T/LH ratio was unaffected by *UGT2B17* genotype.

Despite the fact that serum T seems unaffected by *UGT2B17* genotype, it may influence androgen action at target tissues. Thus, the *UGT2B17* genotype has been associated with fat mass and insulin sensitivity in healthy men independent of circulating T (7). In addition, a homozygous *UGT2B17* deletion has been associated with the risk of prostate cancer in some studies (31). *UGT2B17* enzymatic activity is expressed in normal prostatic tissue from carriers of the *UGT2B17* gene (32, 33), and hypothetically decreased local degradation of DHT in *UGT2B17* del/del subjects may be associated with carcinogenesis in the prostate. However, others failed to demonstrate an association between *UGT2B17* genotype and prostate cancer (33). In line with this, it can be speculated that *UGT2B17* may also be involved in the timing and progression of puberty in males. This is, however, purely speculative at present.

In conclusion, *UGT2B17* genotype certainly affects urinary excretion of androgen metabolites in adolescent males. Even

though circulating T levels are not changed, this polymorphism may hypothetically contribute to the variability of physiological processes that are influenced by androgens, such as puberty.

Acknowledgments

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The Copenhagen Puberty Study was supported by a grant from the Kirsten og Freddy Johansens Foundation. Genetic analyses were partly sponsored by a research grant from the Danish Anti-Doping Agency. The urinary steroid analyses were performed by I. Liborg and financially supported by the Norwegian Ministry of Culture and Church Affairs.

Disclosure Statement: The authors have nothing to declare.

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