Familial resemblance for free androgens and androgen glucuronides in sedentary black and white individuals: the HERITAGE Family Study

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Abstract

Familial correlation analyses were used to evaluate the familial aggregation of plasma androgens and androgen glucuronides (testosterone (TESTO), dihydrotestosterone (DHT), androstane-3α,17β-diol glucuronide (3α-DIOL-G), and androsterone glucuronide (ADT-G)) in 505 members of 99 white families and 296 members of 111 black families participating in the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study. Each of these four measures was determined by RIA after separation of conjugated and unconjugated steroid using C18 column chromatography. All participants were sedentary prior to being including in this study. Significant spouse correlations, as well as parent–offspring and sibling correlations, were found for TESTO, DHT, 3α-DIOL-G, and ADT-G in the white sample, suggesting that common familial environments and genes contribute to the familial resemblance. In the black sample, significant sibling and parent–offspring correlations were found for all four phenotypes, while the spouse correlation was marginally significant for 3α-DIOL-G and not significant for TESTO, DHT, and ADT-G. The non-significance of spouse correlations in the black individuals may be due to the small number of spouse pairs. The maximal heritability estimates of TESTO, DHT, 3α-DIOL-G, and ADT-G were 69%, 87%, 74%, and 56% for white individuals and 70%, 73%, 62%, and 48% for black individuals respectively. Sex differences in heritability estimates were found in the white individuals, but they were less dramatic in the black individuals. In conclusion, plasma levels of androgens and androgen glucuronides are highly heritable in both white individuals and black individuals. There are notable sex differences in the white individuals.

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Introduction

Androgens are synthesized and secreted by the testis and adrenal glands (Lindzey & Korach 1997). Most documented androgen effects occur through binding to specific intracellular receptor proteins (Mooradian *et al.* 1987), with the androgen–receptor complex regulating transcription in target tissues. Androgens, together with other steroids, are critical for sexual differentiation of different target organs and, in adults, are important regulators of many aspects of physiology (Mooradian *et al.* 1987, Lindzey & Korach 1997). Thus, alterations in either the synthesis of androgens and steroid receptors or mutations in the enzymes of the synthetic pathways or in receptors can result in profound clinical pathologies, such as prostate cancer (Reichardt 1999). Recent studies also suggest that variations in plasma androgen levels are associated with other disorders, such as coronary heart disease, obesity, osteoporosis, and the aging process (Alexandersen *et al.* 1996, Tchernof *et al.* 1996, 1997, Gooren 1998, Vanderschueren & Vandenput 2000). Although enzymes that catalyze the conversion and production of steroids are well understood, enzymes that catalyze the conjugation and catabolism of steroids have received less attention.

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Recent studies suggest that glucuronidation plays a prominent role in regulating the levels of androgens. Glucuronidation is a metabolic pathway, by which lipophilic steroids are transferred into more water-soluble molecules, thus enhancing their rates of excretion.

Testosterone (TESTO) is the major androgenic steroid circulating in the blood. Dihydrotestosterone (DHT) is the major active androgen especially in prostatic tissues, which is synthesized from TESTO by 5α-reductase. Androstane-3α,17β-diol glucuronide (3α-DIOL-G) and androsterone glucuronide (ADT-G) are the two major 5α-reduced androgen metabolites, which are regulated by uridine diphosphate glucuronosyltransferase (UGT). Several UGT genes have been identified and mutations have been found (Harding *et al.* 1990, Bélanger *et al.* 1998). It is most likely that TESTO, DHT, 3α-DIOL-G, and ADT-G levels are under some genetic control. However, information on the overall estimate of genetic influences on these androgens and androgen glucuronides is scant, especially in black individuals. In the present study, baseline plasma levels on TESTO, DHT, 3α-DIOL-G, and ADT-G from 505 subjects of 99 sedentary white families and 296 subjects of 111 sedentary black families who participated in the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study were used. The significance of familial resemblance for each of these four androgens and androgen glucuronides was examined by testing the significance of parent–offspring, sibling, and spouse correlations. The relative importance of familial or genetic effects on TESTO, DHT, 3α-DIOL-G, and ADT-G was then assessed using these familial correlations. The findings of this investigation will help us to understand whether genes and/or familial environmental factors contribute to the individual variation in plasma levels of these androgens and will lead us to identify genes (quantitative trait locus) for these traits. A finding of strong familial resemblance would suggest that a family history of abnormal levels of these androgens is a risk for this individual to be abnormal in these hormone levels himself/herself.

The HERITAGE Family Study is a multicenter exercise-training study whose main objective is to assess whether there are changes in cardiovascular, metabolic, and hormonal responses to aerobic exercise training in previously sedentary families and the roles of genetic factors in these changes.

Materials and Methods

Study subjects

The HERITAGE sample, the inclusion criteria and the exclusion criteria have been described in detail elsewhere (Bouchard *et al.* 1995). In brief, parents were required to be 65 years of age or younger, and offspring between 17 and 40 years. Subjects were required to be sedentary at baseline, with a body mass index less than 40 kg/m^2, resting systolic blood pressure less than 160 mmHg, and resting diastolic blood pressure less than 100 mmHg. Subjects were required to be in good physical health in order to complete the 20-week training program.

In all, 99 white nuclear families and 111 black nuclear families with biological parents and offspring enrolled in this study. In each white family, there were often two parents and at least two offspring participating this study, while in each black family there was often only a pair of biological relatives.

Measurements

Two blood samples at least 24 h apart were obtained from an antecubital vein into vacutainer tubes with no anti-coagulant in the morning after a 12-h fast with participants in a semi-recumbent position. For eumenorrheic women, all samples were obtained in the early follicular phase of the menstrual cycle. Only baseline values were examined in the present study.

Fasting plasma was prepared according to a standard protocol. After centrifugation of blood at 2000 ***g*** for 15 min at 4 °C, two aliquots of 2 ml in cryogenic tubes were frozen at 80 °C until shipment. Plasma samples from the three United States HERITAGE Clinical Centers were shipped in the frozen state to the Project Director in Québec who brought them to the HERITAGE Steroid Core Laboratory at the Molecular Endocrinology Laboratory at the Laval University Medical Center for assay.

All steroids were assayed by radioimmunoassay. For non-conjugated steroids, TESTO was differentially extracted with hexane:ethyl acetate (9:1, v:v) and DHT with petroleum ether (35–65 °C).

For glucuronide-conjugated steroids, ethanol extraction was performed followed by C18 column chromatography as described (Bélanger *et al.* 1990, Bélanger 1993). Glucuronide conjugates were submitted to hydrolysis with β-glucuronidase (Sigma Co., St Louis, MO, USA). Steroids from each fraction were further separated by elution on LH-20 columns. Levels of the steroids were measured by radioimmunoassay as previously described (Bélanger *et al.* 1990, Bélanger 1993).

The levels of these androgens and androgen glucuronides were within the normal range for adult men and women (Bélanger *et al.* 1986).

Statistical analysis *Age adjustment* Since the relationship with age might be quite different at different stages of life and since the relationship may also be modulated by sex, adjustments for the effects of age on TESTO, DHT, 3α-DIOL-G, and ADT-G were carried out separately in the four sex-by-generation groups (fathers, mothers, sons, and daughters) using a stepwise multiple regression procedure. Age, age^2, and age^3 were included in the regression model. The significance level for retaining the terms

Table 1 Summary of hypothesis tests

Model	df	Parameter constrained
1. General model	0	All 8 correlations estimated
2. No sex difference in offspring	4	fs=fd, ms=md, ss=dd=sd
3. No sex difference in parents and offspring	5	fs=fd=ms=md, ss=dd=sd
4. No sex and generation difference	6	fs=fd=ms=md=ss=dd=sd
5. No sibling correlations	3	ss=dd=sd=0
6. No parent–offspring correlations	4	fs=fd=ms=md=0
7. No spouse correlations	1	fm=0
8. Sex-specific familial correlations	4	fs=ss, md=dd, fd=ms=sd
9. Same sex vs opposite sex	5	fs=md=ss=dd, fd=ms=sd

in the stepwise regression analysis was 5%. The standardized residuals from the regression analyses were used in the following familial correlation analyses.

Familial correlation model The purpose of the familial correlation analysis was to determine whether there is evidence of familial or genetic factors underlying the variation in each trait (univariate correlation analysis). Significant correlations among siblings and their parents but not between spouses would suggest that there are genetic influences on the trait. Significant spouse correlations, in addition to sibling and parent–offspring correlations, would indicate that the variation is due to both genes and familial environments.

The general univariate correlation model was based on four groups of individuals – fathers (f), mothers (m), sons (s), and daughters (d), leading to eight interindividual correlations (fm, fs, fd, ms, md, ss, sd, dd). The computer program SEGPATH (Province & Rao 1995) was used to estimate the familial correlations based on maximum likelihood methods. The statistical method of analysis fits the model directly to the family data, under the assumption that the phenotypes in a family jointly follow a multivariate normal distribution.

Hypothesis tests The significance of each set of familial correlations is tested by comparing the log likelihood of a reduced model where some of the correlations are fixed to zero against the log likelihood obtained from the general model where all familial correlations are estimated. The likelihood ratio test, which is the difference between minus twice the log likelihoods (-2 lnL) under the two models, is distributed as a χ^2. The degrees of freedoms (df) are given by the difference in the number of parameters estimated in the two nested models. A χ^2 with a P value of less than 0·05 is taken to suggest that the familial correlations set to zero under a null hypothesis are significantly different from zero. In addition to the likelihood ratio test, Akaike's information criterion (AIC) (Akaike 1987), which is -2 lnL plus twice the number of estimated parameters, was used to judge the fit of non-nested models. The best model is indicated by the smallest AIC value. In addition to testing the significance of parent–offspring, sibling, and spouse correlations, five other hypotheses of sex-specific correlations were tested. Table 1 gives a detailed description of each model tested along with the parameter constraints and the degrees of freedom. The familial correlation model as implemented in SEGPATH has been published in detail elsewhere (Rice *et al.* 1997).

Results

Table 2 shows the sample sizes, means, and S.D. values for age, TESTO, DHT, 3α-DIOL-G, and ADT-G by four sex and generation groups separately for white individuals and black individuals. As expected, there were sex and generation differences in TESTO, DHT, 3α-DIOL-G, and ADT-G. Parents had lower levels than offspring, and males had higher levels of all four measures than females in both generations and both races.

The results of the hypothesis tests are summarized in Table 3. Significant spouse correlations (model 7, $P<0{\cdot}01$) in addition to parent–offspring (model 5, $P<0{\cdot}01$) and sibling correlations (model 6, $P<0{\cdot}01$) were observed for all four phenotypes in white individuals, indicating that there is familial aggregation for each and that both genes and familial environment are involved in the familial resemblance. Additional hypotheses were also performed to examine sex and generation differences in the familial correlations (models 2, 3, and 4), sex-specific familial correlations (model 8), and same-sex familial correlations vs opposite-sex familial correlations (model 9). Based on likelihood ratio tests and the AIC index, the most parsimonious models were the general model (model 1) and the sex-specific familial correlation model (model 8) for TESTO and DHT respectively, while the same-sex vs opposite-sex model (model 9) is the most parsimonious model for 3α-DIOL-G and ADT-G. For the black population, sibling and parent–offspring correlations were significant for all four phenotypes while the spouse correlations were not significant for TESTO, DHT, and

Table 2 Characteristics of study variables among 505 white individuals and 296 black individuals from the HERITAGE Family Study by sex and generation groups

		White individuals			Black individuals		
	Group	No.	Mean	S.D.	No.	Mean	S.D.
Variable							
Age (years)	Fathers	95	53·6	5·20	27	50·4	7·22
	Mothers	91	52·2	5·06	56	46·6	6·81
	Sons	153	25·2	5·96	77	27·5	7·27
	Daughters	166	25·4	6·24	136	27·4	7·59
TESTO (nmol/l)	Fathers	94	13·3	5·45	27	13·8	6·97
	Mothers	91	1·15	0·77	56	1·10	0·51
	Sons	153	15·9	5·90	77	16·2	5·96
	Daughters	160	1·46	0·54	136	1·44	0·55
DHT (nmol/l)	Fathers	95	2·20	0·97	27	2·33	0·93
	Mothers	91	0·45	0·21	56	0·50	0·21
	Sons	153	2·78	1·11	76	3·24	1·19
	Daughters	166	0·51	0·21	136	0·61	0·24
3α-DIOL-G (nmol/l)	Fathers	94	23·6	11·7	25	27·0	11·3
	Mothers	90	11·7	5·98	55	11·1	3·66
	Sons	148	32·3	15·1	77	30·6	11·9
	Daughters	164	15·7	8·96	133	15·4	8·01
ADT-G (nmol/l)	Fathers	94	122·3	73·4	24	127·5	63·3
	Mothers	91	64·3	37·3	55	74·2	36·7
	Sons	151	188·8	106·2	76	174·1	55·0
	Daughters	165	106·4	60·7	133	102·1	58·7

Table 3 Results of hypothesis tests for univariate familial correlation analyses of four androgens and androgen glucuronides among 505 white individuals from the HERITAGE Family Study

	df	**χ^2**	***P***	**AIC**	**χ^2**	***P***	**AIC**
	TESTO				DHT		
Model							
1. General model	0	—*	—	16·0	—	—	16·0
2. No sex difference in offspring	4	25·0	<0·01	33·0	50·5	<0·01	58·5
3. No sex difference in parents and offspring	5	25·1	<0·01	31·1	52·6	<0·01	58·6
4. No sex and generation difference	6	33·9	<0·01	37·9	53·7	<0·01	57·7
5. No sibling correlations	3	76·5	<0·01	86·5	144	<0·01	154
6. No parent–offspring correlations	4	45·3	<0·01	53·3	118	<0·01	126
7. No spouse correlations	1	7·27	<0·01	21·3	8·18	<0·01	22·2
8. Sex-specific familial correlations	4	19·9	<0·01	27·9	3·20*	0·53	11·2
9. Same sex vs opposite sex	5	23·6	<0·01	29·6	12·2	0·03	18·2
	3α-DIOL-G				ADT-G		
1. General model	0	—	—	16·0	—	—	16·0
2. No sex difference in offspring	4	12·3	0·01	20·3	7·22	0·12	15·2
3. No sex difference in parents and offspring	5	12·3	0·03	18·3	7·30	0·20	13·3
4. No sex and generation difference	6	14·6	0·02	18·6	8·22	0·22	12·2
5. No sibling correlations	3	92·4	<0·01	102	46·9	<0·01	56·9
6. No parent–offspring correlations	4	61·6	<0·01	69·6	35·0	<0·01	43·0
7. No spouse correlations	1	8·26	<0·01	22·3	6·10	0·01	20·1
8. Sex-specific familial correlations	4	6·11	0·19	14·1	1·62	0·80	9·62
9. Same sex vs opposite sex	5	6·51*	0·26	12·5	1·68	0·89*	7·68

*The most parsimonious model.

Table 4 Results of hypothesis tests for univariate familial correlation analyses of four androgens and androgen glucuronides among 296 black individuals from the HERITAGE Family Study

	df	χ^2	*P*	AIC	df	χ^2	*P*	AIC
	TESTO				DHT			
Model								
1. General model	0	—	—	16·00	0	—	—	16·00
2. No sex difference in offspring	4	1·07	0·90	9·07	4	13·70	0·01	21·70
3. No sex difference in parents and offspring	5	1·30	0·94	7·30	5	13·70	0·02	19·70
4. No sex and generation difference	6	2·35	0·88	6·35	6	15·16	0·02	19·16
5. No sibling correlations	3	24·29	<0·01	34·29	3	22·73	<0·01	32·73
6. No parent–offspring correlations	4	13·25	<0·01	21·25	4	29·12	<0·01	37·12
7. No spouse correlations	1	0·39	0·53	14·39	1	0·67	0·41	14·67
8. Sex-specific familial correlations	4	2·23	0·69	10·23	4	8·03	0·09	16·03
9. Same sex vs opposite sex	5	3·87	0·57	9·87	5	10·01	0·07	16·01
Parsimonious model	7[a]	3·11	0·87	5·11	5[b]	8·09	0·15	14·09
	3α-DIOL-G				ADT-G			
1. General model	0	—	—	16·0	0	—	—	16·0
2. No sex difference in offspring	4	4·88	0·30	12·88	4	2·20	0·70	10·20
3. No sex difference in parents and offspring	5	17·37	<0·01	23·37	5	10·05	0·07	16·05
4. No sex and generation difference	6	18·44	<0·01	22·44	6	10·32	0·11	14·32
5. No sibling correlations	3	15·81	<0·01	25·81	3	9·24	0·02	19·24
6. No parent–offspring correlations	4	23·72	<0·01	31·72	4	13·40	0·01	21·40
7. No spouse correlations	1	3·43	0·06	17·43	1	0	0·99	14·00
8. Sex-specific familial correlations	4	13·48	0·01	21·48	4	8·13	0·09	16·13
9. Same sex vs opposite sex	5	13·74	0·02	19·74	5	8·66	0·12	14·66
Parsimonious model	4[c]	4·88	0·30	12·88	7[d]	10·39	0·17	12·39

[a]Model 4+model 7; [b]model 7+model 9; [c]model 2; [d]model 4+model 7.

ADT-G with a marginal spouse correlation for 3α-DIOL-G (Table 4). While this pattern would generally suggest that genetic factors play more important roles in the familial aggregation for these phenotypes in the black individuals, we believe that the non-significance of spouse correlations in the black individuals is because the number of spouse pairs is very small. Several additional hypothesis tests were also tested for the black individuals. The most parsimonious models were for no sex and generation difference and no spouse correlation (models 4 and 7) for TESTO and ADT-G, the same-sex vs opposite-sex model with no spouse correlation (models 7 and 9) for DHT, and the model with no sex difference in offspring (model 2) for 3α-DIOL-G.

Table 5 presents the familial correlations from the most parsimonious models along with the maximal heritability

Table 5 Parsimonious familial correlations ± S.E. and heritability estimates for four androgens and androgen glucuronides among 505 white individuals from the HERITAGE Family Study

	TESTO	DHT	3α-DIOL-G	ADT-G
Relationship				
Spouse	0·28 ± 0·09	0·34 ± 0·08	0·34 ± 0·08	0·28 ± 0·09
Father–son	0·52 ± 0·07	0·57 ± 0·05	0·51 ± 0·04	0·38 ± 0·05
Mother–daughter	0·30 ± 0·09	0·75 ± 0·03	[0·51]	[0·38]
Father–daughter	0·07 ± 0·09	0·40 ± 0·06	0·37 ± 0·06	0·24 ± 0·06
Mother–son	0·34 ± 0·08	[0·40]	[0·37]	[0·24]
Brother–brother	0·60 ± 0·07	[0·57]	[0·51]	[0·38]
Sister–sister	0·43 ± 0·09	[0·75]	[0·51]	[0·38]
Brother–sister	0·42 ± 0·08	[0·40]	[0·37]	[0·24]
h^2	0·69	0·87	0·74	0·56

Maximal heritability $h^2=(r_{sibling}+r_{parent-offspring})(1+r_{spouse})/(1+r_{spouse}+2r_{spouse}r_{parent-offspring})$, where r represents the inter-individual correlations (see Rice *et al.* 1997). Square brackets indicate that correlations were set equal to a preceeding correlation.

Table 6 Parsimonious familial correlations ± S.E. and heritability estimates for four androgens and androgen glucuronides among 296 black individuals from the HERITAGE Family Study

	TESTO	DHT	3α-DIOL-G	ADT-G
Relationship				
Spouse	[0]	[0]	0·36 ± 0·16	[0]
Father–son	0·35 ± 0·05	0·55 ± 0·10	0·59 ± 0·07	[0·24 ± 0·07]
Mother–daughter	[0·35]	0·41 ± 0·08	0·13 ± 0·09	[0·24]
Father–daughter	[0·35]	0·20 ± 0·10	0·59 ± 0·07	[0·24]
Mother–son	[0·35]	[0·20]	0·13 ± 0·09	[0·24]
Brother–brother	[0·35]	[0·55]	0·37 ± 0·08	[0·24]
Sister–sister	[0·35]	[0·41]	[0·37]	[0·24]
Brother–sister	[0·35]	[0·20]	[0·37]	[0·24]
h^2	0·70	0·73	0·62	0·48

Maximal heritability $h^2=(r_{sibling}+r_{parent-offspring})(1+r_{spouse})/(1+r_{spouse}+2r_{spouse}r_{parent-offspring})$, where r represents the inter-individual correlations (see Rice *et al.* 1997). [0] indicates that the correlation was set to zero, other correlations in square brackets were set equal to a preceeding correlation.

estimates for the white individuals. The maximal heritability for plasma levels of TESTO, DHT, 3α-DIOL-G, and ADT-G were 69%, 87%, 74%, and 56% respectively. For TESTO, heritability was higher in men (91%) than in women (65%) and in opposite-sex pairs (58%). For DHT, heritability was higher in women (∼100%) than in men (88%) and opposite-sex pairs (66%). For 3α-DIOL-G and ADT-G, heritability was higher in same-sex pairs (81% and 65%) than opposite-sex pairs (63% and 43%).

The familial correlations and heritability estimates of all four phenotypes from the most parsimonious models are given in Table 6 for the black individuals. The maximal heritability for plasma levels of TESTO, DHT, 3α-DIOL-G, and ADT-G were 70%, 73%, 62%, and 48% respectively.

Discussion

The present study has indicated that the plasma levels of all four androgens and androgen glucuronides (TESTO, DHT, 3α-DIOL-G, and ADT-G) are highly heritable in both white and black adults. Although genetic and environmental transmission cannot be quantified separately based on the familial correlations, the higher correlations in parent–offspring and sibling pairs than spouse correlations suggest that genes play important roles in the familial aggregation of these four steroids. To the best of our knowledge, the present investigation is the first to quantify the heritabilities for androgens and androgen glucuronides in the black population.

The findings of strong heritabilities for these traits will lead us to identify genes (quantitative trait locus) for these traits, which will facilitate a better understanding of the pathophysiological mechanisms underlying abnormalities for these hormones. Clinically, a high familial resemblance or heritability indicates that a family history of abnormal levels of these androgens are a risk for this individual to be abnormal in these hormone levels himself/herself.

Several heritability studies have been conducted for androgenic steroids in white individuals. Meikle *et al.* (1987) reported that familial factors accounted for 63%, 61%, 56%, and 84% of the variation in plasma levels of TESTO, free (unbound) TESTO, DHT, and 3α-DIOL-G in normal male monozygotic twins. They estimated that approximately 26%, 36%, 12%, and 48% of the variance in plasma TESTO, free (unbound) TESTO, DHT, and 3α-DIOL-G were due to genetic factors. In another study, Meikle *et al.* (1988) found that genetic factors explained approximately 96% and 85% of the variance in DHT and TESTO production rate (also in male twins) and approximately 36% and 4% of the variance in DHT and TESTO clearance rates. A heritability of 60% was also reported for TESTO in a Dutch study of male twins (Harris *et al.* 1998). Significant genetic influences on TESTO, DHT, 3α-DIOL-G, and ADT-G were also reported in a recent study from Québec (Pritchard *et al.* 1998). Previously, only the Dutch study had reported the sex difference in heritability for TESTO. Pritchard *et al.* (1998) reported a heritability of 40% for TESTO in female twins, lower than that in males. To the best of our knowledge, the present investigation is the first to investigate the heritability for ADT-G and to examine the sex differences in heritability for DHT, 3α-DIOL-G, and ADT-G. Our heritability estimates for TESTO, DHT, and 3α-DIOL-G are somewhat higher than those from Meikle's study and the Dutch study. We also found that heritability of TESTO was higher in men than in women, which is in accordance with the Dutch study. Interestingly, we found a higher heritability for DHT in women than in men and in opposite-sex pairs. The reason is unclear. For 3α-DIOL-G and ADT-G, we did not find any difference in heritability estimates between men and

women, but the heritability estimates in same-sex pairs was higher than those in opposite-sex pairs.

The magnitude of heritability estimates for the four phenotypes in the black adults were comparable with those in the white adult population. Additionally, it appears that the sex difference in heritability estimates for these androgens and androgen glucuronides is more pronounced in the white population. This pattern of significant sex difference in heritability estimates in white individuals but not black individuals may be due to smaller number of members in each black family. On average, there were 4·6 and 2·5 members from each white and black family respectively.

The genes related to androgen synthesis and catabolism have been identified. Two enzymes, 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase, are essential for the conversion of dehydroepiandrosterone to TESTO (Lindzey & Korach 1997). It is likely that genes for these two enzymes (Simard *et al.* 1996, Andersson & Moghrabi 1997) play important roles in the genetic variation of TESTO, DHT, 3α-DIOL-G, and ADT-G. Since the heritability for DHT is higher than that for TESTO, the gene for 5α-reductase (Hsieh *et al.* 1991), an enzyme responsible for converting TESTO to DHT, could play a role in the genetic variation observed in blood DHT, 3α-DIOL-G, and ADT-G levels. The same rationale applies to the genes for androgen glucuronidation (Harding *et al.* 1990, Bélanger *et al.* 1998) and the levels of 3α-DIOL-G and ADT-G. Enzymes upstream in the steroid synthetic pathways could also contribute to the genetic variation of these androgens and androgen glucuronidations. The relative importance of these candidate genes can be resolved only by incorporating molecular studies into the present family design.

Because abnormal plasma androgen levels are associated with many disorders such as prostate cancer, coronary heart disease, obesity, osteoporosis, and the aging process (Alexandersen *et al.* 1996, Tchernof *et al.* 1996, 1997, Gooren 1998, Reichardt 1999, Vanderschueren & Vandenput 2000), the present findings and future localization of quantitative trait loci along the chromosomes will undoubtedly lead us to a better understanding of the pathological mechanisms behind these common human diseases.

In conclusion, plasma levels of androgens and androgen glucuronides are highly heritable in both white and black adults and there are sex differences in the heritability of TESTO, DHT, 3α-DIOL-G, and ADT-G, especially in the white population.

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