Genetic effects on serum testosterone and sex hormone-binding globulin in men: a Korean twin and family study

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We conducted a community-based cross-sectional study to evaluate the role of genetics in determining the individual difference in total testosterone and sex hormone-binding globulin levels. Study participants comprised 730 Korean men consisting of 142 pairs of monozygotic twins, 191 pairs of siblings, and 259 father-offspring pairs from 270 families who participated in the Healthy Twin study. Serum concentration of total testosterone and sex hormone-binding globulin were measured by chemiluminescence immunoassay, and free testosterone and bioavailable testosterone were calculated using Vermeulen’s method. Quantitative genetic analysis based on a variance decomposition model showed that the heritability of total testosterone, free testosterone, bioavailable testosterone, and sex hormone-binding globulin were 0.56, 0.45, 0.44, and 0.69, respectively after accounting for age and body mass index. Proportions of variance explained by age and body mass index varied across different traits, from 8% for total testosterone to 31% for sex hormone-binding globulin. Bivariate analysis showed a high degree of additive genetic correlation (ρa = 0.67) and a moderate degree of individual-specific environmental correlation (ρe = 0.42) between total testosterone and sex hormone-binding globulin. The findings confirmed the important role of genetics in determining the individually different levels of testosterone and sex hormone-binding globulin during adulthood in Korean men as found in non-Asian populations, which may suggest that common biologic control for determining testosterone level directly or indirectly through binding protein are largely shared among different populations.

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INTRODUCTION
Testosterone, a male sex hormone primarily secreted from the testes, has been suggested to be associated with the aging process, sexual function, and various health conditions, including cardiovascular, endocrine, and bone health in men.1 Testosterone levels vary between individuals even in the same ethnic population.2–4 Evidence from twin studies and family studies indicates that genetics contributes to the inter-individual variation in testosterone levels,4,9 in addition to age and a range of health conditions.2,8 However, most previous studies included only the Caucasians and the reported heritability (h2) of testosterone levels varies across studies, ranging from very mild (h2 = 0.2) to very strong (h2 = 0.7) for total testosterone (TT)5–12 and from 0.19 to 0.60 for free testosterone.10–13 In addition, the hitherto reported levels of testosterone heritability have been obtained mostly from twin-only studies or nontwin family studies. Although studies involving twins can discriminate genetic influences from environmental influences, the estimated heritability from a twin-only study tends to be inflated, because it includes dominant genetic effects in addition to additive genetic effects which are the main interest.14 Inclusion of more diverse family relationship such as father-offspring pairs who share same additive genetics but do not share dominant genetics at all would provide much better chance of testing dominant genetic component as well as shared environmental components.

The clinical action of testosterone largely depends on the level of free or bioavailable testosterone rather than TT, because 50% to 60% of TT is bound to sex hormone-binding globulin (SHBG). SHBG also exhibits wide inter-individual variation, and diverse factors contribute to the regulation of SHBG, which makes the study of testosterone more complicated.15,16 Therefore, it seems necessary to know the influence of genetics on SHBG, which confounds the understanding of how SHBG controls testosterone levels and its effects on health.16,17

We conducted this study in 730 Korean men from extended families composed of twins and their brothers and fathers to investigate the contributions of genetic factors to TT, functional testosterone, and SHBG and to understand the relationship between testosterone and SHBG.

MATERIALS AND METHODS
Study subjects
Study subjects included 730 Korean men consisting of 142 pairs of monozygotic (MZ) twins, 191 pairs of siblings, and 259 father-offspring pairs, 191 pairs of siblings, and 259 father-offspring pairs.
pairs from 270 families who participated in the Healthy Twin study between April 2005 and April 2010. Dizygotic twins were included in the sibling group, because the level of genetic resemblance between dizygotic twins is similar to that between non-twin brothers, and the number of DZ twins was too small (33 pairs) to be analyzed as a separate group. Details of the study design and protocols have been previously published. In brief, the Healthy Twin study is a community-based cohort study ongoing since 2005, which has recruited Korean adult twins and their first-degree adult family members without ascertainment of their health status, through a nationwide advertisement and a mailing to some members of the Korean twin-family register whose contact information was available. During the first and second wave surveys between April 2005 and April 2010, a total of 742 men with at least one more male family member underwent measurement of blood levels of testosterone and SHBG. Among these, 12 men with a cancer history or a testosterone treatment were not included. All participants provided written informed consent. The Institutional Review Board of each participating center approved the study protocol.

**Study variables**

Blood samples were drawn in the morning (around 10 a.m.) after overnight fasting. Serum was immediately separated and stored at ~70°C. We measured TT and SHBG immediately after thawing the frozen serum by electrochemiluminescence immunoassay using commercial ADVIA Centaur XP (Siemens, Erlange, Germany) for TT and a MODULAR ANALYTICS E170 analyzer (Roche, Basel, Switzerland) for SHBG. The minimum concentration measurable at the laboratory was 0.35 nmol L\(^{-1}\) for TT and SHBG. Inter-assay coefficients of variation were <7.6% for TT and <2% for SHBG. Albumin levels in fresh sera were measured by colorimetry using an ADVIA 1650 chemistry analyzer (Siemens). Free testosterone (cFT) and bioavailable testosterone (cBAT) levels were calculated using Vermeulen’s method. 

Body mass index (BMI) was calculated using measured weight and height (kg m\(^{-2}\)). Information on health habits was obtained using a self-administered questionnaire.

We ascertained the zygosity of twin pairs using 16 short tandem repeat markers including one sex-determining marker for 67% of twin pairs and a self-administered zygosity questionnaire for the remaining 33%. Ascertainment of zygosity using the questionnaire was 94.3% accurate compared to ascertainment by the short tandem repeat marker. 

**Statistics**

The characteristics of offspring and fathers were compared by t-test and Chi-square test and intraclass correlation coefficients (ICCs) between various intra-familial pairs were estimated using linear mixed regression analysis using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Quantitative genetic analysis was conducted using Sequential Oligogenic Linkage Analysis Routines (SOLAR) version 2.0 (Southwest Foundation for Biomedical Research, San Antonio, TX, USA). To eliminate the influence of skewness and residual kurtosis, inverse normal transformation was performed for TT, SHBG, cFT, and cBAT before they were entered into the analytic models.

A variance component approach was used to partition the total phenotypic variation (6\(p^2\)) of each trait into its additive genetic component (6\(a^2\)) and unmeasured environmental component (6\(e^2\)). In addition, unmeasured shared environmental components within a family (6\(c^2\)) were tested and added to the model if adding 6\(c^2\) effect significantly increased overall model fitting in terms of likelihood compared with models without 6\(c^2\) (i.e., increase in 2ln(L) > 2, L: likelihood). The key assumption of this model is that the effects of environmental factors are common to the members of a family and that the three factors, 6\(a^2\), 6\(c^2\), and 6\(e^2\), have independent and additive effects on the trait variance with the total residual variance being the sum of the additive and individual-specific variance components (6\(p^2 = 6a^2 + 6c^2 + 6e^2\)). Heritability represents the proportion of residual variance attributed to additive genetic factors (6\(a^2/6p^2\)). By using the strength of twin and family design, we tried to estimate narrow-sense heritability, instead of the broad-sense heritability that includes both dominant genetic effects and additive genetic effects as usually estimated from twin-only studies.

We also estimated the additive genetic correlations between TT and SHBG by performing a bivariate variance-component-based genetic analysis to ascertain evidence of a common genetic regulation of the traits. Through the bivariate variance-component analysis, the phenotypic correlations between two traits are partitioned into genetic (\(\rho_g\)) and environmental (\(\rho_e\)) correlations. Thus, this provides insight as to whether or not the correlation between two or more phenotypes of an individual is codetermined by shared genes and environment.

**RESULTS**

Table 1 shows the characteristics of the study subjects. Compared with their fathers, offspring had higher levels of cFT and cBAT and lower SHBG levels. Current alcohol drinking and smoking were more prevalent, and participation in an adequate level of physical exercise was less prevalent among offspring than among their fathers (Table 1).

Table 2 shows the age-adjusted intraclass correlation coefficients (ICCs) between various intra-familial pairs and heritability

| Characteristics                          | Offspring | Father | P*  |
|------------------------------------------|-----------|--------|-----|
|                                         | Monozygotic| Siblings*|     |
| Number of subjects (persons)             | 284 (142 pairs) | 305 | 141 |
| Age, mean (s.d.) (years)                 | 38.4 (7.4) | 41.3 (9.3) | 65.7 (5.8) | <0.001 |
| BMI, mean (s.d.) (kg m\(^{-2}\))         | 24.4 (2.7) | 24.7 (3.0) | 24.1 (2.7) | 0.07 |
| Albumin, mean (s.d.) (g l\(^{-1}\))     | 47.1 (2.7) | 46.3 (3.3) | 44.8 (3.0) | <0.001 |
| Testosterone, mean (s.d.) (nmol l\(^{-1}\)) | 19.9 (7.0) | 20.6 (7.4) | 20.3 (7.5) | 0.87 |
| Sex hormone-binding globulin, mean (s.d.) (nmol l\(^{-1}\)) | 39.5 (17.0) | 42.1 (19.7) | 62.0 (27.3) | <0.001 |
| cFT, mean (s.d.) (nmol l\(^{-1}\))      | 0.4 (0.1) | 0.4 (0.1) | 0.3 (0.1) | <0.001 |
| cBAT, mean (s.d.) (nmol l\(^{-1}\))     | 9.5 (3.2) | 9.4 (3.2) | 7.0 (2.3) | <0.001 |
| Smoking habit (%)                        |            |        |     |
| Current smoker                           | 56.7       | 59.0   | 39.7 | <0.001 |
| Ex-smoker                                | 16.6       | 19.0   | 29.1 |
| Never smoker                             | 26.8       | 22.0   | 31.2 |
| Alcohol drinking habit (%)               |            |        |     |
| Current drinker                          | 77.5       | 86.2   | 62.4 | <0.001 |
| Ex-drinker                               | 7.8        | 5.6    | 12.8 |
| Never drinker                            | 14.8       | 8.2    | 24.8 |
| Physical exercise (%)                    |            |        |     |
| Regular-adequate (≥3/week)               | 23.9       | 15.7   | 36.9 | <0.001 |
| Regular-inadequate (1–2/week)            | 18.3       | 15.1   | 9.2  |
| None                                     | 57.8       | 69.2   | 53.9 |

Data were presented as mean (s.d.) or percentage. *Comparisons between offspring and father were done by the t-test or Chi-square test, s.d.: standard deviation; BMI: body mass index; cBAT: calculated bioavailable testosterone; cFT: calculated free testosterone
estimates for each trait. The ICC between MZ twin pairs was moderately high for all traits (between 0.51 and 0.61), and was around twice as high as the ICC estimates for sibling pairs and father-offspring pairs. However, the ICC estimates for sibling pairs were similar to those for father-offspring pairs.

Age-adjusted heritability was moderately high for all traits (between 0.44 and 0.59) with the highest estimate being that of SHBG. When BMI was additionally adjusted, the heritability of SHBG was increased by 10%. Proportions of variance explained by covariates varied across different traits, from 8% for TT to 31% for SHBG. When we further adjusted for health behaviors such as smoking, alcohol, and regular physical activity, the estimated heritability was almost unchanged.

Table 3 shows the cross-trait correlations between SHBG and TT. There was a moderately high ($P < 0.01$) positive phenotypic correlation between TT and SHBG. When the phenotypic correlation between SHBG and TT was decomposed, both additive genetic and unique environmental correlations were statistically significant ($P < 0.05$). These finding did not change materially when BMI was adjusted in addition to age.

**DISCUSSION**

Although studies including ours have consistently suggested an important genetic influence on individual differences in TT and SHBG levels at adulthood, the reported heritability estimates range widely. The difference in adjusted covariates, the extent of involved intra-familial relationships, ethnicity, or the age range of studied participants may explain the variability in reported heritability.

Classical twin studies have reported heritability estimates of 22%–59% in males,$^{10,13,15}$ which are slightly lower than the heritability of 40%–73% found in family-based studies.$^{9,10,13,14}$ Heritability estimates in study involving both twins and their families may be lower compared to twin-only study or family-only study by avoiding overestimation of heritability through the comparisons of phenotypic correlations between various familial relationships.$^{14}$ However, the heritability estimates of TT and SHBG in our twin and family study were similar to those in twin-only or family-based studies.

Most previous studies were conducted in Caucasian populations$^{6,10–13,25}$ with only three studies including Mexican-Americans$^{15,23}$ or African-Americans.$^{9,25}$ In our study, the heritability estimates for testosterone and SHBG were similar to or higher than those found in Caucasians. However, it is unclear whether the genetic role is stronger in Asian men due to the lack of other Asian studies.

Only a few studies have accounted for covariates.$^{10,13,15}$ Adiposity has been found to be inversely associated with TT and SHBG.$^{13,26}$ We found that heritability estimates of SHBG and TT increased substantially after adjusting for BMI while the study by Bogaert et al.$^{13}$ found that heritability estimate of TT decreased and that of SHBG increased after adjusting for BMI. Although we could not elucidate the reason for the different findings between our study and the study by Bogaert et al.,$^{13}$ we think that the difference supports the importance of BMI adjustment, especially when comparisons are made between populations with different BMI distributions.

Considering that the variance explained by covariates other than age and BMI was only about 1% in our study, it seems less likely that the differences in adjustment for lifestyle factors between studies have contributed to a lot to the variation of heritability estimates for TT and SHBG between studies.

Previous studies have reported wide range of heritability estimates for TT and SHBG by the age range of study participants with very low heritability at birth$^{27}$ and higher heritability in adolescents$^{23}$ and adults.$^{5,13}$ These findings seem to suggest that inter-individual variability of TT is determined mainly by environmental factors in early infancy$^{27,28}$ while the influence of genetic factors becomes more evident in older age.$^{10}$

Supporting the role of genetic factors in determining individual differences in TT and SHBG levels in men, genome-wide association studies (GWAS) and meta-analysis revealed several SNPs associated with TT levels$^{6,29–31}$ and SHBG levels$^{30,31,32}$ at several genomic regions. However, most studies were conducted in the Caucasians, and many of the identified SNPs in the Caucasian studies$^{6,29}$ were not repeatedly identified in Chinese study.$^{33}$ Therefore, studies are needed to identify more pleiotropic loci, especially in Asians and other non-Caucasian populations. In addition, clinical relevance of genetically determined individual differences in the levels of testosterone and SHBG should be further evaluated, considering that the SNP on the SHBG gene that seems to determine testosterone level was not associated with the risk of cardiovascular and metabolic diseases associated with low testosterone level in a study.$^{32}$

Polymorphisms in the genes encoding the enzymes involved in TT biosynthesis and metabolism may also contribute to inter-individual variability of testosterone.$^{33}$

Although controversial findings exist,$^{34,35}$ androgen receptor CAG repeat polymorphism has been found to be involved in determining inter-individual variability of circulating testosterone and SHBG level, probably through negative feedback mechanism.$^{36–38}$

**Table 3: Cross-trait correlation (95% CI) between sex hormone-binding globulin and total testosterone**

| Adj usted covariates | Phenotypic correlation | Additive genetic correlation* | Individual-specific environmental correlation* |
|----------------------|------------------------|-------------------------------|-----------------------------------------------|
| Age                  | 0.63 (0.58–0.67)       | 0.67 (0.60–0.73)              | 0.53 (0.42–0.62)                              |
| Age and BMI           | 0.60 (0.55–0.64)       | 0.67 (0.61–0.72)              | 0.42 (0.30–0.53)                              |

*Estimated by bivariate analysis. 95% CI: 95% confidence interval; BMI: body mass index

**Table 2: Intraclass correlation coefficients and heritability of testosterone and sex hormone-binding globulin**

| Intraclass correlation coefficients (95% CI) | Age-adjusted | Age and BMI-adjusted | Age, BMI, and life-style adjusted |
|---------------------------------------------|--------------|----------------------|----------------------------------|
|                                             | h² (s.e.)    | VAR (%)              | h² (s.e.)                        | VAR (%)                        |
| Monozygotic twin (n=142 pair)               |              |                      |                                 |                                |
| Sibling pair (n=191 pair)                   |              |                      |                                 |                                |
| Father-offspring pair (n=259 pair)          |              |                      |                                 |                                |

| Trait                          | Total testosterone | Sex hormone-binding globulin | cFT | cBAT |
|--------------------------------|---------------------|-----------------------------|-----|------|
| h² (s.e.)                     | 0.54 (0.45–0.62)    | 0.51 (0.42–0.59)            | 0.52 (0.43–0.60) | 0.51 (0.41–0.59) |
| VAR (%)                       | 0.53 (0.06)         | 0.49 (0.06)                 | 0.45 (0.06)     | 0.44 (0.06)      |

*Dizygotic twins were combined into sibling group; Smoking, alcohol consumption, and physical exercise. 95% CI: 95% confidence interval; h² (s.e.): heritability (standard error); VAR (%): proportion of variance explained by covariates; BMI: body mass index; cBAT: calculated bioavailable testosterone; cFT: calculated free testosterone.
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Genetic effect on male sex hormones

J Sung and YM Song

790

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