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Genetic determinant of trabecular bone score (TBS) and bone mineral density: A bivariate analysis

Lan T. Ho-Pham [a,*], Didier Hans [c], Minh C. Doan [b], Linh D. Mai [b], Tuan V. Nguyen [a,d,e,f]

[a] Bone and Muscle Research Group, Ton Duc Thang University, Ho Chi Minh City, Vietnam
[b] Department of Rheumatology, People's Hospital 115, Ho Chi Minh City, Vietnam
[c] Center of Bone Disease, Lausanne University Hospital, Lausanne, Switzerland
[d] Bone Biology Division, Garvan Institute of Medical Research, Sydney, Australia
[e] School of Public Health and Community Medicine, UNSW, Australia, Sydney
[f] University of Technology Sydney (UTS), NSW, Australia

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SUMMARY

This study sought to estimate the extent of genetic influence on the variation in trabecular bone score (TBS). We found that genetic factors accounted for ~45% of variance in TBS, and that the co-variation between TBS and bone density is partially determined by genetic factors.

Introduction: Trabecular bone score has emerged as an important predictor of fragility fracture, but factors underlying the individual differences in TBS have not been explored. In this study, we sought to determine the genetic contribution to the variation of TBS in the general population.

Methods: The study included 556 women and 189 men from 265 families. The individuals aged 53 years (SD 11). We measured lumbar spine bone mineral density (BMD; Hologic Horizon) and then derived the TBS from the same Hologic scan where BMD was derived. A biometric model was applied to the data to partition the variance of TBS into two components: one due to additive genetic factors, and one due to environmental factors. The index of heritability was estimated as the ratio of genetic variance to total variance of a trait. Bivariate genetic analysis was conducted to estimate the genetic correlation between TBS and BMD measurements.

Results: TBS was strongly correlated with lumbar spine BMD ($r = 0.73$; $P < 0.001$). On average TBS in men was higher than women, after adjusting age and height which are significantly associated with both TBS and lumbar spine BMD. The age and height adjusted index of heritability of TBS was 0.46 (95% CI, 0.39–0.54), which was not much different from that of LSBMD (0.44; 95% CI, 0.31–0.55). Moreover, the genetic correlation between TBS and LSBMD was 0.35 (95% CI, 0.21–0.46), between TBS and femoral neck BMD was 0.21 (95% CI, 0.10–0.33).

Conclusions: Approximately 45% of the variance in TBS is under genetic influence, and this effect magnitude is similar to that of lumbar spine BMD. This finding provides a scientific justification for the search for specific genetic variants that may be associated with TBS and fracture risk.

1. Introduction

Trabecular bone score (TBS), as the terminology implies, is an index of bone fragility. TBS was derived from the dual energy X-ray absorptiometry image to describe skeletal texture of microarchitecture [1]. Several studies have shown that lower values of TBS were associated with increased risk of fragility fracture [2], and more importantly, the association was independent of bone mineral density (BMD) and age [3]. The independent contribution of TBS to fracture risk prediction suggests that a measurement of TBS could improve the accuracy of fracture risk assessment for an individual [4,5].

Despite the emerging role of TBS in fracture risk assessment, the etiology of TBS has been less well documented. In population based studies, TBS is strongly related to lumbar spine BMD, with the coefficient of correlation ranging between 0.6 and 0.7 [6,7]. As with BMD, TBS is inversely related to advancing age and positively associated with greater body mass index [6]. Moreover, the distribution of TBS closely follows a normal (bell-shaped) distribution with an almost constant variance across populations. It is likely that the bell-shaped distribution of TBS is a result of effects arising from segregating alleles at multiple loci. Thus, it could be reasonably hypothesize that the between-individuals variation in TBS is partially determined by hereditary factors.

The present study was designed to test the above hypothesis. Our primary aims were to determine the relative contributions of genetic

* Corresponding author at: Bone and Muscle Research Group, Ton Duc Thang University, 19 Nguyen Huu Tho Street, Tan Phong Ward, Ho Chi Minh City, Vietnam.
E-mail address: hophamthuclan@tdt.edu.vn (L.T. Ho-Pham).

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and environmental factors to the between-individual variation in TBS. We also tested the hypothesis that the co-variation between TBS and BMD is partly determined by shared genetic factors.

2. Study design and methods

2.1. Study design

This study was part of the Vietnam Osteoporosis Study (VOS) which was initiated in mid-2015. VOS is designed as a population based, long-term and prospective study, with the setting being the Ho Chi Minh City (formerly Saigon). The City is a major economic hub of the ASEAN region, with a population of 8.2 million. The study's procedure and protocol were approved by the research and ethics committee of the People's Hospital 115. The study was conducted according to the ethical principles of the Declaration of Helsinki, and all participants gave written informed consent.

The inclusion criteria were men and women aged between 20 and 90 years, who agreed to participate in the Study. We excluded individuals who were deemed to have impaired cognitive function or were not willing to give informed consent or were physically unable to complete clinical tests.

We used two approaches to recruit participants. In the first approach, we contacted community organizations to solicit a list of members, and from the list we ran a computer program to randomly selected individuals who met the age and gender criteria. A letter was then sent to the selected individuals to invite them and their family members to participate in the Study. In the second approach, we recruited participants via television, the Internet, and flyers in universities. The flyers described (in Vietnamese) the study's purposes, procedures, and benefits of participants. Individuals agreed to participate in the study were then transported to the Bone and Muscle Research Laboratory at the Ton Duc Thang University for clinical assessment and evaluation. The participants did not receive any financial incentive, but they received a free health check-up, and lipid analyses.

2.2. Measurements

Each participant was administered with a structured questionnaire by a trained interviewer. The questionnaire solicits information concerning clinical history, medication use, lifestyle factors, history of falls and fractures, and anthropometric factors. Height and weight were measured by an electronic portable, wall-mounted stadiometer (Seca Model 769; Seca Corp, CA, USA) without shoes or ornaments or hats or heavy layers of clothing. Body mass index (BMI) was derived as the weight in kilograms divided by the square of the height in meters.

Participants were also asked to provide information on current and past smoking habits. Alcohol intake in average numbers of standard drinks per day, at present as well as within the last 5 years, was obtained. Clinical data including blood pressure, pulse, and reproductive history (i.e. parity, age of menarche and age of menopause), medical history (i.e. previous fracture, previous and current use of pharmacological therapies) were also obtained. Two blood pressure measurements were taken (5 min apart) in seated position, and the mean of two measurements was taken as the individual's blood pressure. Individuals were classified as having hypertension if their average systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.

2.3. Bone mineral density and TBS measurements

Areal BMD was measured at the lumbar spine, femoral neck, total hip and whole body using a Hologic Horizon (Hologic Corp, Bedford, MA, USA). For the lumbar spine, we measured BMD from L2 to L4. The densitometer was standardized by phantom before each measurement. The measurement was done by a qualified radiology technologist. Based on 20 individuals, the coefficient of variation in BMD at our lab was 1.5% for the lumbar spine and 1.7% for the hip. Fat mass and lean mass were derived from the whole body scan.

TBS measurements were performed in the Bone Disease Center at the Lausanne University Hospital, Lausanne, Switzerland (TBS iNsight Software, version 2.1; Medimaps, Merignac, France). These analyses were performed blind to fracture status and any clinical parameters. The software uses the antero-posterior spine raw image(s) from the densitometer, including the BMD region of interest and edge detection so that the TBS calculation is performed over exactly the same region of interest as the BMD measurement. In the current analysis, we used a research version of the commercialized TBS iNsight software, which allows for large batched analyses from a workstation. The short term reproducibility of TBS determinations as been reported in several monocenter studies ranges from 1.1%–1.9% CV [8].

2.4. Data analysis

The raw data were stored in two separate files: the pedigree file contains all ID of an individual and the individual's father and mother, and the phenotype file contains all demographic and clinical data identified by an individual's ID. The two files were matched by individuals' unique ID to construct a family based dataset for further analysis.

We used the multiple linear regression method to model the relationship between TBS or BMD and potential determinants. The determinants considered in the analysis were gender, age, height, weight, and BMI. In order to assess the relative importance of each predictor, we used the "LMG" method [9] to decompose the overall R^2 into individual effect. The R program [10] was used to estimate the relative contribution of individual predictor variable.

The primary objective of analysis was to estimate the index of heritability (H^2) of TBS and lumbar spine BMD. The secondary objective was to determine the genetic and environmental correlations between TBS and lumbar spine BMD. In order to estimate H^2, the variance of a trait (V_p) was decomposed into two components: one due to genetic factors (V_g) and one due to environmental factors (V_e): $V_p = V_g + V_e$. Then, $H^2 = V_g / V_p$.

In order to estimate the variance components, we consider the value of each trait of an individual (y_i) as a function of the overall average (μ), the pedigree/family of the individual and its environment or random errors:

$$y_i = \mu + g_i + e_i$$

where g_i is the random deviations from μ for individual i that are due to additive genetic factors, and e_i represents residual error effects, accounting for the rest of the variation. It is assumed that g_i is independent from e_i. It is further assumed that g_i are normally distributed with mean 0 and variance-covariance $G * V_g$, where G is the matrix of genetic coefficients which are determined by the pedigree specific structure. For

Table 1
Characteristics of 556 women and 189 men.

Variable	Women	Men	*P*-value
Number of subjects	556	189	
Age (years)	54.1 (11.5)	53.0 (12.4)	0.307
Height (cm)	152.0 (5.3)	162.5 (6.5)	<0.001
Weight (kg)	53.4 (8.0)	62.2 (11.6)	<0.001
Body mass index (kg/m^2)	23.1 (3.2)	23.5 (3.7)	0.327
Lumbar spine BMD (g/cm^2)	0.86 (0.14)	0.94 (0.16)	<0.001
Femoral neck BMD (g/cm^2)	0.66 (0.11)	0.74 (0.14)	<0.001
Whole body BMD (g/cm^2)	0.98 (0.11)	1.06 (0.11)	<0.001
Trabecular bone score	1.31 (0.11)	1.37 (0.09)	<0.001
Lifestyle factors			
Current smokers (%)	2.9	47.6	<0.001
Regular alcohol use (%)	3.4	43.0	<0.001

Note: Values in brackets are standards deviation.

Table 2
Determinant of trabecular bone score and lumbar spine BMD: Multiple linear regression analysis.

Variable and determinant	Regression coefficient (standard error)	Relative importance (%)
TBS (trabecular bone score)		
Gender (male)	0.029 (0.013)	2.3
Age (+5 year)	−0.025 (0.002)	22.7
Height (+1 cm)	0.001 (0.0007)	2.9
Lumbar spine BMD		
Gender (male)	0.061 (0.015)	3.9
Age (+5 year)	−0.026 (0.003)	12.7
BMI (+1 kg/m^2)	0.010 (0.002)	5.4
Femoral neck BMD		
Gender (male)	0.068 (0.012)	6.6
Age (+5 year)	−0.027 (0.003)	18.5
BMI (+1 kg/m^2)	0.009 (0.001)	6.9
Whole body BMD		
Gender (male)	0.093 (0.015)	8.2
Age (+5 year)	−0.026 (0.003)	12.6
BMI (+1 kg/m^2)	0.010 (0.0018)	5.9

All regression coefficients are statistically significant at $P < 0.001$.

example, full-siblings or parent-offspring would have a coefficient of 0.5, and identical twins would have the coefficient of 1. Moreover, e_i are assumed to follow a normal distribution with mean 0 and variance V_e. The likelihood of each trait of the family members is assumed to follow a multivariate normal distribution with the variance-covariance matrix that is a function of the coefficient of relationship between individuals.

We used a Bayesian approach to estimate the model parameters. In the Bayesian approach, each parameter must be associated with a probability distribution which reflects our "belief" about each parameter's possible values. In this analysis we used a non-informative prior for each parameter. For the variance, we used the inverse gamma distribution as a prior. The prior distribution was then combined with the likelihood of the data to derive the posterior distribution for each model parameter. We used the R package MCMCglmm [11] to estimate the posterior distribution of each parameter.

In order to estimate the proportion of covariance between TBS and BMD is explained by genes common to both traits, we conducted bivariate genetic analyses. The pairs of traits considered in the analysis were TBS and lumbar spine BMD, TBS and femoral neck BMD, and TBS and whole body BMD. In this analysis, the variance-covariance matrix of two traits is decomposed into genetic and environmental components based on the familial correlation structure. Accordingly, the genetic correlation between TBS and BMD was determined by the ratio of covariance between TBS and BMD over the product of the standard deviation of TBS and the standard deviation of BMD. The environmental correlation between TBS and BMD was derived in the same manner. The genetic and environmental correlations were adjusted for age, gender, and BMI.

3. Results

The study included 745 individuals from 265 families. Most (91%) families are full siblings. The average (SD) age of participants was 53.8 (11.7) years, and there was no statistically significant difference between men and women in terms of age distribution. There was also no significant difference between groups in terms of body mass index. However, as expected, men had significantly greater BMD measurements than women (Table 1).

The variation in TBS was significantly associated with gender, age, and body height (Table 2). On average, TBS were 4.5% higher in men than in women (Fig. 1). Advancing age was significantly associated with lower TBS measurements, such that each 5 years increase in age was associated with a 0.025 decrease in TBS. Each centimeter increase in body height was associated with 0.001 unit increase in TBS. Collectively, the three factors (gender, age and height) accounted for ~28% of total variance in TBS. Relative importance analysis indicate that most of the explained variance was accounted by advancing age.

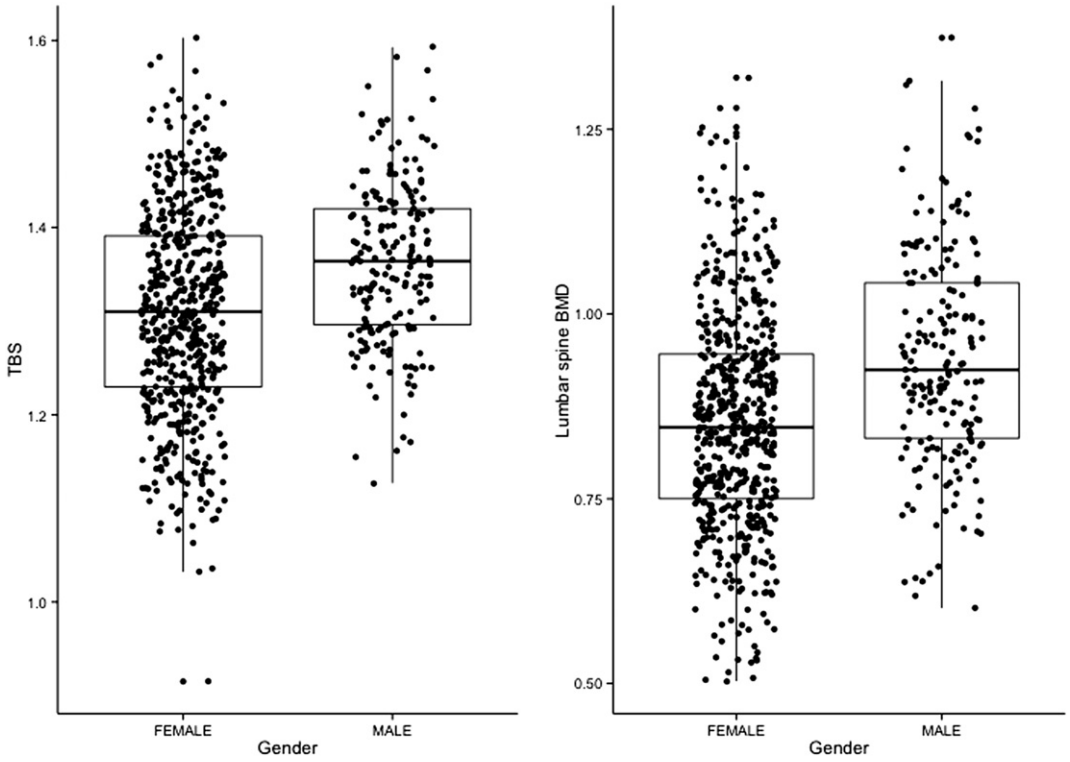

Fig. 1. Distribution of trabecular bone score (left panel) and lumbar spine BMD (right panel) by gender. On average, men had greater TBS and LSBMD than women.

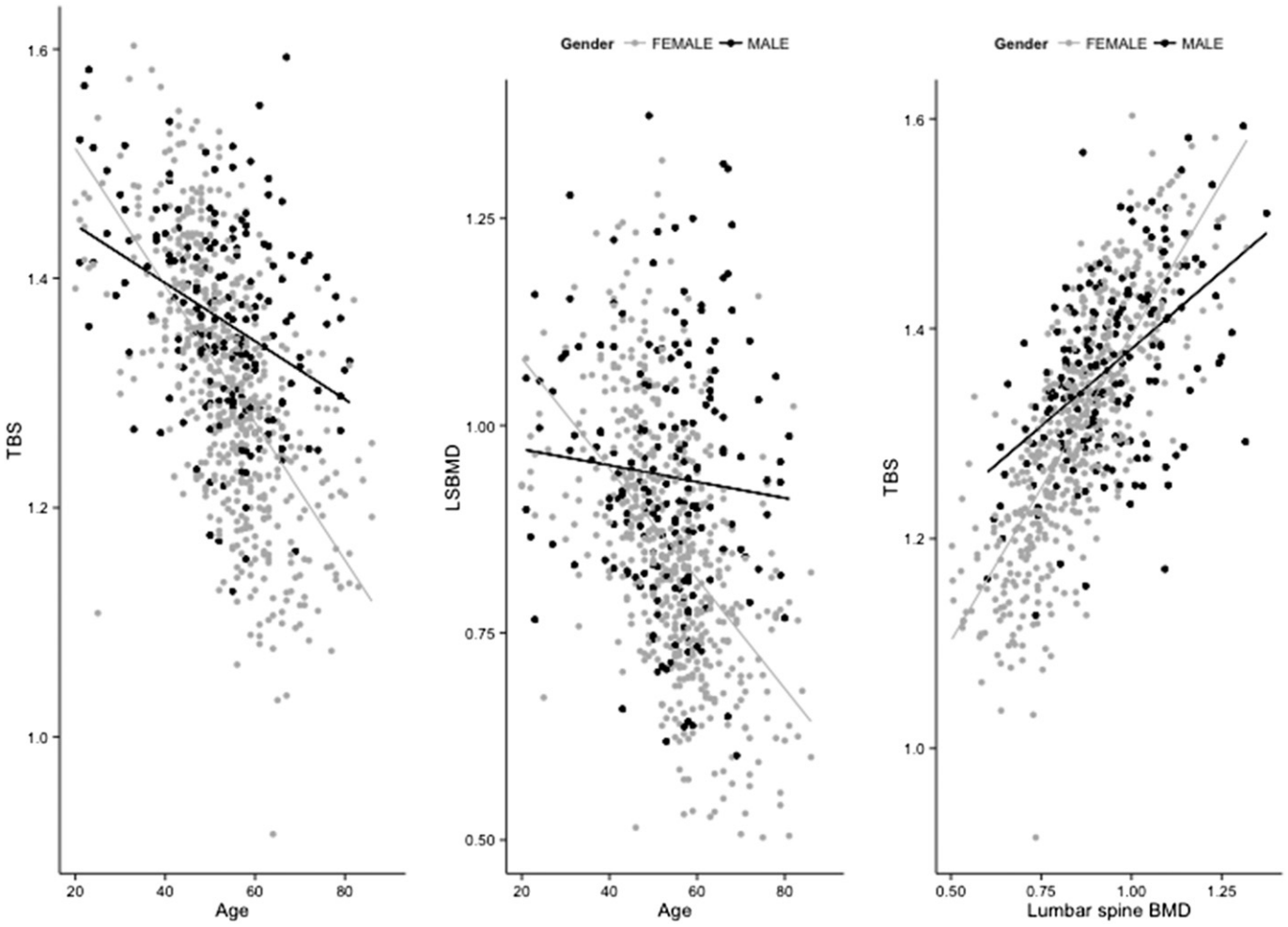

Fig. 2. Relationship between age and TBS (left panel), age and LSBMD (middle panel), and TBS and LSBMD (right panel) stratified by gender.

There was a significant and positive correlation between TBS and LSBMD (Fig. 2). The correlation between lumbar spine BMD and TBS was high ($r = 0.72$; $P < 0.001$), and this correlation appears to be greater in women ($\boldsymbol{r = 0.74}$) than men ($\boldsymbol{r = 0.58}$). Bone mineral density at the lumbar spine, femoral neck, and whole body was significantly associated with gender, age, and body mass index (BMI). The three factors collectively "explained" 22%, 32%, and 27% of total variance in lumbar spine, femoral neck, and whole body BMD, respectively (Table 2), with age being the most important factor.

Results of biometric modeling of variance in TBS and BMD are show in Table 3. In unadjusted analysis, genetic factors accounted for 51% (95% CI, 44% to 58%) of total variance in TBS. However, after adjusting for age, gender and body height, the index of heritability slightly reduced to 46% (95% CI, 39% to 54%). The unadjusted index of heritability of lumbar spine BMD was 53% (95% CI, 42% to 60%); and this was reduced to 44% (95% CI, 31% to 55%) after adjusting for age, gender, and BMI. The variation in femoral neck BMD had a strong genetic component, with the adjusted index of heritability being 71%, which is greater than that in whole body BMD (43%).

Table 3
Index of heritability (median and 95% credible interval) of trabecular bone score and bone mineral density measurements.

Variable	Univariate analysis	Adjusted for gender, age and height (or BMI)
Trabecular bone score	0.51 (0.44–0.58)	0.46 (0.39–0.54)[1]
Lumbar spine BMD	0.53 (0.42–0.60)	0.44 (0.31–0.55)
Femoral neck BMD	0.77 (0.57–0.90)	0.71 (0.47–0.95)
Whole body BMD	0.66 (0.43–0.90)	0.43 (0.26–0.60)

[1] Adjusted for age, gender and height.

In the next analysis, we estimated the genetic and environmental correlation between TBS and BMD after adjusting for covariates (Table 4). The covariance between TBS and BMD was determined by genetic factors, with the genetic correlation being 0.35 (95% CI, 0.21–0.46). The environmental correlation (0.39; 95% CI, 0.26–0.48) was slightly higher than the genetic correlation. The genetic correlation between TBS and femoral neck BMD (0.21), or between TBS and whole body BMD (0.19), was lower than between TBS and lumbar spine BMD. It is noted that the unadjusted phenotypic correlation between TBS and femoral neck BMD (0.57), and between TBS and whole body BMD (0.48) was lower than that between TBS and lumbar spine BMD (0.72).

4. Discussion

TBS has emerged as an independent predictor of fragility fracture, with the magnitude of association being equivalent to that of bone mineral density. However, etiological determinants of TBS have not been well documented. In this family based study, we have demonstrated that approximately 45% of the between-individual variance in TBS was determined by genetic factors, after adjusting for age, gender and height. Moreover, the about one third of the covariation between TBS and lumbar spine BMD was also genetically determined.

To our knowledge, this is the first demonstration of the heritability of TBS, and it is thus difficult to put the present study's finding within context. However, the index of heritability of LSBMD in this study is

Table 4
Genetic and environmental correlation between TBS and BMD measurements.

	Phenotypic correlation	Genetic correlation[1]	Environmental correlation[1]
TBS and lumbar spine BMD	0.72 (0.67–0.76)	0.35 (0.21–0.46)	0.39 (0.26–0.48)
TBS and femoral neck BMD	0.57 (0.51–0.63)	0.21 (0.10–0.33)	0.18 (0.10–0.34)
TBS and whole body BMD	0.48 (0.40–0.55)	0.19 (0.02–0.30)	0.16 (0.05–0.29)

[1] Adjusted for gender, age, and BMI. Phenotypic correlations are not adjusted for covariates. Values are coefficient of correlation and 95% confidence interval.

lower than previous twin studies'. Classical twin sties [12,13] have typically shown that the index of heritability for lumbar spine BMD ranged between 75% and 92%. In this study, we found that the heritability was much lower (51%). This difference is somewhat expected, because it is well known that twin studies tend to over-estimate the effect of genetic factors of a trait [14]. In the classical twin model, the shared environmental factors are assumed to be equal between monozygotic and dizygotic twins, and as a result, the heritability is often higher than in siblings based studies.

It is still unknown whether the heritability of TBS is resulted from polygenic effects or a single major gene effect. However, the biometric model that we used in the estimation of heritability assumes that the variation in each of the traits is determined by a mean plus a polygenic background. Therefore, the data are consistent with this assumption, which means that the variation in TBS between individuals is more likely to be determined by multiple genes.

Apart from genetic factors, we found that the variation in TBS was also related to gender, age, and body height. On average, men had greater TBS than women, and the difference was 0.6 standard deviation. The difference was independent of age, gender, and height. It is not clear why men had greater TBS value than women, but it is noted that TBS is strongly correlated with lumbar spine BMD, and lumbar spine BMD is greater in men than in women. By using the approach of "relative importance" in the multiple regression analysis [10], we were able to assert that age is the most important determinant of TBS. Age alone accounted for almost 23% of total variance in TBS, and this attributable proportion was almost 10 times greater than the effect of either gender or height.

The finding of heritability of TBS has important implications in osteoporosis research. This finding provides a rationale for the search for specific genes that determine the variation in TBS between individuals. Strategies of gene search have shifted from candidate gene association to genomewide association analysis (GWAS), and more recently whole genome sequencing. The success of GWAS in the identification of common genetic variants associated with BMD can also be applied to search for specific genes that determine the variation in TBS. This study provides an important clue. Because the relationship (as measured by the covariance) between TBS and LSBMD is under genetic regulation, it can be hypothesized that the two traits are more likely to share some common genetic variants.

The present findings should be considered within context of strengths and weaknesses. The study was based on a reasonably large sample size of multiple families which allow a better estimation of genetic parameters. The measurement of TBS was done with a state of the art method. However, the study was mainly based on full-siblings and two-generation, which provide less genetic relationship for a more refine estimate of heritability. The sample size for the male group was modest, which limited the sex and gene interaction or genetic – environmental interaction analyses.

In summary, the present study has shown that approximately 45% of the TBS variance is attributable to genetic factors, and that this effect is equivalent to the genetics of lumbar spine BMD. More interestingly, we showed that TBS and lumbar spine BMD are more likely to share common genetic variants, and this suggests that a genomewide search for genes associated with TBS is a worthwhile effort.

Author contributions

Conceived and designed the experiments: LHP, TVN. Performed the experiments and data collection: LHP, DH, LDM, MCD, TVN. Analyzed the data: TVN, LHP. Wrote the paper and interpretation of data: LHP, TVN.

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Competing interests

The authors have declared that no competing interests exist.

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References

[1] L. Pothuaud, P. Carceller, D. Hans, Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: applications in the study of human trabecular bone microarchitecture, Bone 42 (4) (2008) 775–787.
[2] E.V. McCloskey, A. Oden, N.C. Harvey, W.D. Leslie, D. Hans, H. Johansson, et al., A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX, J. Bone Miner. Res. (2015).
[3] J.T. Schousboe, T. Vo, B.C. Taylor, P.M. Cawthon, A.V. Schwartz, D.C. Bauer, et al., Prediction of incident major osteoporotic and hip fractures by trabecular bone score (TBS) and prevalent radiographic vertebral fracture in older men, J. Bone Miner. Res. (2015).
[4] N.C. Harvey, C.C. Gluer, N. Binkley, E.V. McCloskey, M.L. Brandi, C. Cooper, et al., Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice, Bone 78 (2015) 216–224.
[5] E.V. McCloskey, A. Oden, N.C. Harvey, W.D. Leslie, D. Hans, H. Johansson, et al., Adjusting fracture probability by trabecular bone score, Calcif. Tissue Int. 96 (6) (2015) 500–509.
[6] W.D. Leslie, M.A. Krieg, D. Hans, Manitoba Bone Density P. Clinical factors associated with trabecular bone score, J. Clin. Densitom. 16 (3) (2013) 374–379.
[7] A.C. Looker, N. Sarafrazi Isfahani, B. Fan, J.A. Shepherd, Trabecular bone scores and lumbar spine bone mineral density of US adults: comparison of relationships with demographic and body size variables, Osteoporos. Int. (2016).
[8] B.C. Silva, W.D. Leslie, H. Resch, O. Lamy, O. Lesnyak, N. Binkley, et al., Trabecular bone score: a noninvasive analytical method based upon the DXA image, J. Bone Miner. Res. 29 (3) (2014) 518–530.

[9] U. Gromping, Relative importance for linear regression in R: the package relaimpo, J. Stat. Softw. 17 (1) (2006) 1–27.
[10] U. Grömping, Estimators of relative importance in linear regression based on variance decomposition, Am. Stat. 61 (2007) 139–147.
[11] J.D. Hadfield, MCMC methods for multi{response generalised linear mixed models: the MCMCglmm R package, J. Stat. Softw. 33 (2) (2010) 1–22.
[12] N.A. Pocock, J.A. Eisman, J.L. Hopper, M.G. Yeates, P.N. Sambrook, S. Eberl, Genetic determinants of bone mass in adults. A twin study, J. Clin. Invest. 80 (3) (1987) 706–710.
[13] T.V. Nguyen, G.M. Howard, P.J. Kelly, J.A. Eisman, Bone mass, lean mass, and fat mass: same genes or same environments? Am. J. Epidemiol. 147 (1) (1998) 3–16.
[14] O. Zuk, E. Hechter, S.R. Sunyaev, E.S. Lander, The mystery of missing heritability: genetic interactions create phantom heritability, Proc. Natl. Acad. Sci. U. S. A. 109 (4) (2012) 1193–1198.