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ORIGINAL ARTICLE

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High heritability of bone size at the hip and spine in Chinese

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Abstract Bone size, an independent determinant of bone strength, is an important risk factor for osteoporotic fracture. In the present study, we investigated the magnitude of the genetic determination of bone size at the spine and hip and their genetic covariation (if any) in a population of Chinese residing in Shanghai City of P.R. China. The subjects were 50 healthy full-sib pairs of females, 188 mother-daughter pairs, and 128 husband-wife pairs selected from 401 nuclear families. Bone size (centimeters squared) was measured at the spine and hip by dual-energy X-ray absorptiometry (DEXA). The narrow-sense heritabilities h^2 (SE) of bone size at the spine and hip were 0.63 (0.14) and 0.45 (0.14) respectively when estimated by full-sib pairs, and 0.60 (0.07) and 0.69 (0.07) respectively when estimated by mother-daughter pairs. Marginally significant genetic correlation was observed between the spine and hip bone size. The significantly and moderately high h^2 values for bone size demonstrated in this study warrant a subsequent genetic study to search for the genes or genomic regions underlying the phenotype in Chinese.

Keywords Bone size · Heritability · Genetic correlation · Spine and hip

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Introduction

Osteoporotic fracture (OF) is a major cause of morbidity and mortality in the elderly and is a significant concern with a rapidly growing aging population. The aging demographic trend alone could cause the number of hip fractures worldwide to increase from an estimated 1.7 million in 1990 to 6.3 million in 2050, with most of world's future fractures happening in Asia (Cooper et al. 1992). In recent years, with the increased aging Chinese population, more attention has been paid to OF in China (Liu et al. 2002).

Most linkage and association studies of OF to date have focused on the genetic contributions to bone mineral density (BMD). However, the importance of bone size has been underestimated in most studies. Some studies have demonstrated that the size and geometry of a bone also determines its mechanical strength and predicts the risk of fracture independent of BMD (Lotz et al. 1990; Cordey et al. 1992; Gilsanz et al. 1995; Tabensky et al. 1996; Cheng et al. 1997; Edmondston et al. 1997). It also has been shown that the variation of bone size in Caucasians may be under the control of genetic determination, and some genes may play a genetic role in bone size (Moller et al. 1978; Flicker et al. 1996; Heaney et al. 1997; Deng et al. 2002a). The study of Need et al. (1996) indicated that the BB genotype of the Bsm I polymorphism in the vitamin D receptor (VDR) gene was associated with lower BMD and larger bone areal size in men, and the lower BMD may be due to larger bone size rather than reduced bone mass. Gong et al. (1999) demonstrated that parathyroid hormone (PTH) gene polymorphism accounted for about 7–9% of the total variances of bone dimensional variables. However, it is not known as to what extent genetic factors may impact the variation of bone size in Chinese. It is also not clear whether different skeletal sites share a common genetic determination in Chinese.

The goal of the present study is to estimate the magnitude of the narrow-sense heritability (h^2) and

genetic covariation, if any, of bone size at the spine and hip in Chinese first-degree relative pairs. Since h^2 may be overestimated when not taking the effect of common living environment into account in the relative-pair analyses, we also tested whether there existed common familial environmental effects on the covariation of bone size for family members.

Materials and methods

Subjects

Study subjects were selected from 401 nuclear families used in our earlier study (Qin et al. 2003), which was approved by the Research Administration Departments of Shanghai's Sixth People's Hospital and Hunan Normal University. All subjects were recruited from Shanghai local residents. They were all of the Han ethnicity, which is greater than 93% of the total Chinese population. Enrollment was finished in 13 months. For each study subject, we obtained information on age, gender, gynecological and medical history, etc. All subjects signed informed-consent documents before entering the project. Exclusion criteria were used to minimize any known potential confounding factors on the study phenotypes as detailed by Deng et al. (2002b), and they were assessed by gaining information from nurse-administered questionnaires and/or medical records. Briefly, patients with chronic diseases/conditions that may potentially affect bone mass were excluded. These diseases/conditions included chronic disorders involving vital organs (heart, lung, liver, kidney, brain), serious metabolic diseases (diabetes, hypo- or hyperparathyroidism, hyperthyroidism), other skeletal diseases (Paget's disease, osteogenesis imperfecta, rheumatoid arthritis), chronic use of drugs affecting bone metabolism (corticosteroid therapy, anticonvulsant drugs), and malnutrition conditions (chronic diarrhea, chronic ulcerative colitis).

For the h^2 and genetic correlation estimation, we selected 50 independent female full-sib pairs (only one pair from each family) and 188 mother-daughter pairs. The full-sib pair subjects were all premenopausal aged 20–43 and had regular menstrual cycles. Among the mother-daughter pair subjects, 160 mothers were postmenopausal and had ceased menses for at least 12 months; the other 28 mothers and 188 daughters were premenopausal. To estimate the effect of the common household environment on the variation of bone size between family members, 128 couple pairs, who were not genetically related, were analyzed. The couple group was divided into two subgroups according to the wives' age. One group ranged from 51 to 60 years; the other ranged from 61 to 70 years. The 128 wives were all postmenopausal. The 284 nuclear families comprised of 902 subjects were used to estimate the common household effect on bone size. The basic characteristics of the study subjects are shown in Table 1.

Measurement

Since the OFs typically occur at the hip and spine (Dennison and Cooper 2000), we chose these two sites to measure quantitative phenotypes. For the spine, our quantitative phenotype was the combined bone projected area of L1–L4; for the hip, it was the combined bone projected area of the femoral neck, trochanter, and intertrochanteric region. Bone size (centimeters squared) was measured by posteroanterior (PA) scanning using a Hologic QDR 2000+ dual-energy X-ray absorptiometry (DEXA) (Hologic Inc., Bedford, MA, USA) for each subject. The machine was calibrated daily, and the reproducibility was assessed by performing repeated scans (five times) of seven normal individuals. The coefficient of variability (CV) values of the DEXA measurements for bone size at the spine and the hip were 0.06% and 1.18% respectively. The weight and height of each subject was measured at the time of the DEXA measurement.

Statistical analyses

Statistical analyses were performed using the SAS (Statistical Analysis System software version 6.12, SAS Institute, Inc. Cary, NC, USA) and SOLAR (Sequential Oligogenic Linkage Analysis Routines software version 2.0.3) available at http://www.sfbr.org/sfbr/public/software/solar/. Stepwise multiple linear regression analyses showed that gender (male and female: denoted by "1" and "2"), age, menopausal status (premenopausal and postmenopausal: denoted by "1" and "2"), height, and weight respectively, had significant effects on bone size in different subgroups. These significantly confounding factors were adjusted for each subject in the different subgroups according to the results of stepwise multiple linear regression analyses (all equations listed in Table 2), and the significant covariates were also taken into account in analyses by SOLAR.

h^2 was estimated using $2r_{fs}$ and $2r_{m-\mathrm{d}}$ (Lynch and Walsh, 1997)

$$h^2 = \frac{\sigma_A^2}{\sigma_P^2} \approx \frac{2Cov_{fs}}{\sigma_P^2} = 2r_{fs} \quad (1)$$

$$h^2 = \frac{\sigma_A^2}{\sigma_P^2} \approx \frac{2Cov_{m-d}}{\sigma_P^2} = 2r_{m-d} \quad (2)$$

where r_{fs} and $r_{m\text{-}d}$ are the phenotypic correlations between full sibs and between mothers and daughters at the same anatomic site respectively. σ_A^2 is the additive genetic variance and σ_P^2 is the total phenotypic variance. Cov_{fs} and $Cov_{m\text{-}d}$ are covariances between full-sib pairs and between mother-daughter pairs respectively (Deng et al. 1999). The 95% confidence intervals of r_{fs}, $r_{m\text{-}d}$ and thus h^2 were obtained via Fisher's z-transformation. The significance of r_{fs} and $r_{m\text{-}d}$ was examined by a t test (Sokal and Rohlf 1981). We used two methods to estimate the genetic correlation (r_s) of spine and hip bone size: (1) the same method as in our previous study on BMD (Deng et al. 1999):

Table 1 Basic characteristics of subjects

Subjects	Size (n)	Age (years)	Height (cm)	Weight (kg)	Bone size (cm^2)	
					Spine	Hip
Mothers	188	58.7 ± 6.3	154.5 ± 5.7	58.4 ± 8.5	53.99 ± 5.34	32.42 ± 3.29
Daughters	188	30.6 ± 5.7	159.8 ± 5.3	55.2 ± 7.9	57.94 ± 4.88	31.87 ± 3.01
Full sibs	100	32.8 ± 4.8	160.3 ± 4.8	56.5 ± 7.6	58.18 ± 4.56	32.51 ± 3.21
Wife of the 1st couple pair	73	55.6 ± 2.5	156.5 ± 5.5	59.8 ± 9.2	54.76 ± 5.17	32.84 ± 3.19
Husband of the 1st couple pair	73	59.4 ± 4.5	167.2 ± 5.3	69.9 ± 9.1	65.54 ± 4.53	41.36 ± 4.17
Wife of the 2nd couple pair	55	64.3 ± 2.9	152.9 ± 5.3	58.7 ± 8.3	52.98 ± 5.53	32.44 ± 3.45
Husband of the 2nd couple pair	55	66.2 ± 4.1	164.9 ± 6.0	68.0 ± 10.2	62.69 ± 6.88	40.98 ± 3.73

All values are raw data (mean ± standard deviation). Couple pairs are divided into two subgroups according to age of wives. Age of wives in the 1st and 2nd age group is 51–60 and 61–70 respectively

Table 2 Equations of stepwise multiple linear analyses in different subgroups. *S, H, A, W, M,G*: bone size, height, age, weight, menopausal status, gender

Subject group	Equations of stepwise multiple linear analyses
Full–sib pairs	Spine $S=-40.15+0.614H$*
	Hip $S=-17.71+0.289H$*$+0.119A$**
Mother-daughter pairs	Spipe $S=-37.27+0.600H$*$-0.768M$**
	Hip $S=-26.12+0.346H$*$+0.089A$
1st couple pairs group	Spine $S=-20.23+0.469H$*$+0.105W$*$-4.679G$*
	Hip $S=-31.13+0.433H$*$-3.865G$*
2nd couple pairs group	Spine $S=-65.21+0.774H$*
	Hip $S=-9.60+0.259H$*$+0.115W$*$-4.364G$*

Age of wives in the 1st and 2nd age groups is 51–60 and 61–70 respectively. *$P<0.01$. **$P<0.05$

Table 3 Narrow-sense heritability (h^2) and 95%CI at the spine and hip. *SE* standard error, *CI* confidence interval of h^2

Subjects	Spine		Hip	
	$h^2 \pm$ SE	95%CI	$h^2 \pm$ SE	95%CI
Full-sib pairs	0.63 ± 0.14	0.43–0.77	0.45 ± 0.14	0.20–0.65
Mother-daughter pairs	0.60 ± 0.07	0.50–0.68	0.69 ± 0.07	0.61–0.76

$$r_g \approx \frac{\mathrm{cov}(X_1, Y_2) + \mathrm{cov}(X_2, Y_1)}{2\sqrt{\mathrm{cov}(X_1, X_2)\mathrm{cov}(Y_1, Y_2)}} \quad (3)$$

where X and Y denote the spine and hip bone size. The numerator is the covariance between one trait (X) in one group of relative pairs, and the other trait (Y) is the counterpart of the relative pairs. The covariances in the denominator are those between the same trait (X or Y) in one group of relative pairs and the counterpart of the relative pairs. (2) We also performed maximum likelihood-based bivariate variance decomposition analyses using the SOLAR statistical package. Variance decomposition methods were used to estimate both the genetic and environmental correlation between the spine and hip bone size in our 284 nuclear families. A likelihood ratio test was used as a model-fitting technique for the comparison between the general model and a more limited one (constraining the genetic or environmental correlation value to zero).

The phenotypic correlation between genetically unrelated couples living in the same household for the same anatomic site can be estimated from the Pearson product-moment correlation coefficient (r); r approximately reflects the magnitude of the phenotypic resemblance of people living in the same household. To validate this approximate estimate further, we also tested the common household effect within the nuclear families from which all our subjects were selected. (The unqualified subjects were not taken into account in the analyses.) Univariate variance decomposition analyses were performed using SOLAR software when the household effect was taken into account. The significant level of all analyses was set to $P \leq 0.05$.

Results

The results of analyses for h^2 are presented in Table 3. For the spine, h^2 (±SE) estimated by analyses of full-sib pairs and mother-daughter pairs was 0.63 (±0.14) and 0.60 (±0.07) respectively. For the hip, h^2 (±SE) was 0.45 (±0.14) and 0.69 (±0.07) according to full-sib pairs and mother-daughter pairs respectively. Results from the two different analyses suggest that about 45–70% of bone size variation at the hip and spine was attributable to genetic determination in our samples.

Table 4 Genetic and environmental correlation between spine and hip bone size. *SE* standard error

Model	Genetic correlation ($r \pm$ SE)	Environmental correlation ($r \pm$ SE)	χ^2 (P)
General	0213 ± 0.108	0.115 ± 0.116	-
Constrained 1	0.000*	0.288 ± 0.06	3.584 (0.058)
Constrained 2	0.296 ± 0.062	0.000*	0.945 (0.331)

In the Constrained 1 and Constrained 2 models, we presumed there was no genetic or environmental correlation respectively. * Parameter is constrained to zero

Table 5 Results of the estimate of common household effect on bone size. *SE* standard error

Subjects	Spine size		Hip size	
	Phenotypic correlation	P value	Phenotypic correlation	P value
1st group of couple pairs	0.018	0.880	0.152	0.199
2nd group of couple pairs	−0.082	0.553	0.152	0.269
	Household variance ± SE	P value	Household variance ± SE	P value
Nuclear families	0.025 ± 0.074	0.369	0.096 ± 0.080	0.115

Age of wives in the 1st and 2nd age groups is 51–60 and 61–70 respectively. Phenotypic correlation is the r value of the Pearson product-moment correlation coefficient between the adjusted bone size values of wives and husbands. Household variance is the proportion of the phenotypic variance that can be explained by household effect

The phenotypic correlations (cross-correlations) between hip size in one group of relative pairs and spine size in the counterpart of relative pairs, mother-daughter pairs, or full-sib pairs, were not significant. The genetic correlation between hip and spine size was 0.140 estimated from the mother-daughter pairs and 0.048 according to full-sib pairs. Results of bivariate variance decomposition analyses of spine and hip bone size estimated from the 284 nuclear families are shown in Table 4. The genetic correlation between spine and hip bone size is marginally significant, and the environmental correlation is not significant.

Results of the common household effect on bone-size variance are shown in Table 5. Phenotypic correlations between wives and husbands in the two subgroups were not significant after adjustment for gender, age, weight, and height. Univariate variance decomposition analyses

in nuclear families also demonstrated that the variance of the common household effect was small and not significant at either the spine or the hip.

Discussion

The predisposition of OF is heterogeneous. Many other factors have an important impact on bone fragility apart from low BMD. Among them, bone size is an independent risk factor for OF. Bigger bone size is a logical adaptation to enhance the mechanical competence of bone, because a larger cross-sectional area can bear larger compressive loads and cope more efficiently with bending loading. It has been shown that patients with spinal fractures often have smaller vertebrae size (Mazess et al. 1994; Gilsanz et al. 1995; Vega et al. 1998) and that bone sizes at different sites have different optimum architectural characteristics to adapt to mechanical loads (Cheng et al. 1997). In order to search for genes underlying the variation of bone size, it is necessary for us to first discuss the magnitude of genetic determinants.

In the present study, h^2 was estimated by first-degree relatives. Compared to broad-sense heritability (H^2), h^2 is the proportion of total phenotypic variation, which is due to the additive effects of genes and can be transmitted to the next generation. The additive variance is the chief cause of resemblance between relatives and is the major determinant of observable genetic properties of the population (Falconer and Mackay 1996). Therefore, h^2 is more useful than H^2.

We found that genetic factors explained about half of the variation of bone size in our Chinese female samples after adjusting the confounding effects of age, height, weight, and menopausal status. These results were in close concordance with the estimation made in Caucasians (Deng et al. 2002a). h^2 of hip bone size estimated from mother-daughter pairs was higher than that estimated from full-sib pairs, while the results for the spine were similar according to the two different samples. There are two possible reasons to explain hip discrepancies. First, the dominant genetic variation may not play a significant role for bone-size variation at the hip, and it will not result in a higher estimate for h^2 using full-sib pairs. Second, the sample size was small, and the samples were different when estimated from full-sib pairs and mother-daughter pairs, which may have resulted in sampling errors. Sensitivity to sampling errors for the h^2 estimate may be different at the spine and hip. The difference of the hip h^2 estimate may be insignificant when sampling errors are taken into account.

We should be prudent to consider the results of genetic correlation analyses using formula (3) above. This is because we got no significant cross-correlations when using the mother-daughter pairs and full-sib pairs analyses. Moreover, r_s is vulnerable to sampling errors (Falconer and Mackay 1996), which may cause imprecise results when using a small sample size (such as the sib-pairs analyses in our study). Therefore, results of bivariate analyses estimated from the 284 nuclear families by SOLAR analyses may be preferable. Results of marginally significant genetic correlation and nonsignificant environmental correlation by bivariate analyses indicated that the variation of spine and hip bone size was under the impact of different genetic or environmental factors. This result may be explained by the characteristics of these two different anatomic sites. Spine and hip architecture is definitely different. Moreover, the proportions of trabecular and cortical bone at these two sites are different, and the physiological activities of trabecular and cortical bone are different when bone develops. All these factors may indicate that different sets of genes (or other genetic factors) and environmental factors may account for the differentiation of development of bone architecture at the spine and hip.

Although this study is the first to evaluate heritability of bone size in Chinese, the potential limitations in our study should be mentioned. First, DEXA has been accepted as a clinic method to measure bone size, with the advantage of a relatively low cost and small radiation dose compared to quantitative computed tomography (QCT) (Kalender et al. 1992; Genant et al. 1996). However, DEXA bone measurement size here is projected bone area (centimeters squared), not volumetric bone size (centimeters cubed). Second, estimation of heritability using relative pairs may be inflated by common environmental effects (Lynch and Walsh 1997).

In order to validate the h^2 estimate, we tested the common household effect on the variation of bone size using two methods: (1) by univariate variance decomposition analyses in our nuclear families, and (2) by simple correlation analyses on the variation of bone size in couple pairs. Significant phenotypic correlation within genetically unrelated age-matched couple pairs was most attributed to shared environmental factors. Because we divided the couple pairs into two subgroups, the period of shared common living for each couple pair was similar in each subgroup. For the first subgroup, the duration of common living was 25–35 years, and it was 35–45 years for the second subgroup. The insignificant correlations between age-matched couple pairs suggested that common familial environment may have little impact on the resemblance of bone size between the couples. Another thing that should be pointed out is using couple pairs to evaluate environmental effects on bone size. Bone size is almost completely established during childhood and adolescence. The effect of common household environment between elderly couples may be little. However, excluding the possible phenotypic correlation between couple pairs and the nonsignificant common household effect in nuclear families partially validate our h^2 estimates. Finally, the h^2 estimation in our study was performed in female full-sib pairs and mother-daughter pairs, which indicates that the h^2 results can be representative only of females. However, since females are more vulnerable to OF, our results still

have great significance in further genetic studies of bone phenotypes. In the future, further studies involving other types of relatives would be worthwhile for the detection of possible nonadditive genetic effects of dominance or epistasis and effects of common living environment.

In conclusion, our study revealed a high degree of heritability of bone size at the spine and hip in a Chinese population, which establishes the foundation for further genetic research on searching for causative genes of bone size in Chinese.

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