Letter to the Editor

Genetic and Environmental Effects on the Bone Development of the Hand and Wrist in Chinese Young Twins

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We assessed genetic and environmental effects on bone development of the hand and wrist, and on key anthropometric measures in Chinese young twins. In total, 139 monozygotic and 95 dizygotic twin pairs aged from 5 to 18 years were recruited. The twin correlations of total hand and wrist scores for monozygotic (MZ) and dizygotic (DZ) twins were 0.71 and 0.36, respectively. Bivariate model analysis showed moderate genetic correlations only for total skeletal maturity *vs.* weight and total skeletal maturity *vs.* waist circumference (r, 0.51 and 0.46, respectively). Our findings demonstrated that genetic factors played important roles in bone development of the hand and wrist in Chinese young twins, and that these genetic effects might be distinct from those influencing anthropometric measures.

Bone age is a measure of developmental age, or physiological maturity. As such, it more closely represents biological age than chronological age, and provides a measure of how far an individual has progressed towards full maturity. Assessment of bone age is a clinical procedure used in pediatric radiology to evaluate skeletal maturity (also termed 'bone age') on the basis of radiographically determined bone growth in the left hand and wrist[1]. In China, a skeletal maturity evaluation standard was applied in 1992 to assess skeletal maturity using bone growth in the left hand and wrist[2]. This standard was then revised in 2006[3] in accordance with the TW3 Bone Age Determination Method widely used outside China[4].

Final height predictions of normally growing children, followed up until they reached their parents' height, showed that genetic factors were of importance in skeletal maturity. Estimating the heritability of bone age could quantify or partition the genetic and environmental effects on bone development. In our study, young twins were selected from the Qingdao Twin Registry in China, and used skeletal radiographs to obtain the bone maturity scores. Some anthropometric measures were also collected to estimate heritability characteristics of these specific bones, and to explore the genetic determinants of growth.

Children and adolescents aged 5-18 years were selected from the Qingdao Twin Registry (QTR), part of the Chinese National Twin Registry[6-7], as the candidate subjects. Subjects with chronic diseases, disorders of body weight or stature, or osteonecrosis, serious metabolic disease, chronic use of drugs affecting bone metabolism, and malnutrition conditions, were excluded. A total of 12 cases (2.5% of the sample) were excluded from this study. As a result, 234 twin pairs with normal skeletal development remained in the study. The twins' parents gave written informed consent prior to the imaging and anthropometric measures.

Bone development was evaluated in accordance with the standards of skeletal maturity of hand and wrist bone age for the Chinese issued by the Physical Culture and Sports Commission of the People's Republic of China in 2006[3]. Radiographs were obtained with an x-ray generator (Polyphos 50; Siemens, Erlangen, Germany) at 60 kVp and 1.2 mAs, and each radiograph of the hand and wrist was obtained with a rigorous data collection protocol[8]. Anthropometric measures were performed at the time of the imaging examination. For the twins of the same sex and blood type, zygosity was determined by using 16 short tandem repeat markers[9].

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Table 1 presents the skeletal maturity scores of the hand and wrist, and the anthropometric measures that were assessed. The average scores of nine bones of the hand and wrist in female subjects were significantly higher than those in males (P<0.001). For the other five bones, scores were significantly higher in males (P<0.01). The average total skeletal maturity score for females was significantly higher than those for males (P<0.001).

Intra-class correlation coefficients for the monozygotic (MZ) and dizygotic (DZ) groups, and univariate and bivariate genetic analyses were performed with Mx software using the raw data option and standard structural equation modeling methods. In model-fitting analyses, the total variance was decomposed into additive genetic effects (A), common (shared) environmental effects (C), and unique environmental effects (E). As the study sample was relatively small, a full ACE model was selected. Twin correlations and proportion of variances from univariate ACE models are shown in Table 2. Twin correlations of the hand and wrist scores in the MZ group ranged from 0.26 to 0.82, while for DZ twins they ranged from 0.01 to 0.38. Twin correlations of total hand and wrist scores for MZ and DZ groups were 0.71 and 0.36, respectively. Twin correlations for anthropometric measures in MZ twins were all above 0.71 and even in DZ twins most were around 0.50.

The estimated heritability for total hand and wrist scores was 69% with 95% confidence interval (CI) 37%-78%. Unique environment effects were important for the Capitate, Hamate, Metacarpal V and Radius with the proportion of variance being over 50%. Of the estimated heritability of anthropometric measures, sitting height had the highest heritability, with proportion of variance of 94% (80%-95%); this was followed by shoulder breadth, body mass index and height. The proportion of variance from the unique environment effects ranged from 4% to 33%, and was far lower than that attributed to genetic effects.

Table 1. Description of Skeletal Maturity Scores of the Hand and Wrist, and Anthropometric Measures

Content	All	Female (n=231)	Male (n=237)	P^*
Skeletal maturity score				
Radius	67 (13.9)	65 (12.3)	68 (15.2)	<0.001
Metacarpal I	26 (11.9)	37 (6.4)	16 (4.4)	<0.001
Metacarpal III	42 (12.0)	50 (9.8)	35 (9.1)	<0.001
Metacarpal V	59 (14.1)	61 (12.1)	56 (15.5)	<0.001
Proximal Phalanx I	24 (9.3)	32 (6.0)	17 (4.4)	<0.001
Proximal Phalanx III	77 (20.1)	73 (15.0)	80 (23.7)	0.007
Proximal Phalanx V	57 (15.4)	64 (13.0)	51 (14.8)	<0.001
Middle Phalanx III	62 (13.8)	65 (12.2)	59 (14.6)	<0.001
Middle Phalanx V	21 (11.3)	31 (6.3)	11 (3.7)	<0.001
Distal Phalanx I	73 (16.5)	69 (12.9)	76 (18.8)	0.005
Distal Phalanx III	54 (12.1)	57 (10.7)	51 (12.5)	<0.001
Distal Phalanx V	20 (7.7)	26 (4.5)	13 (3.3)	<0.001
Capitate	78 (22.5)	73 (16.6)	84 (26.0)	<0.001
Hamate	91 (19.3)	82 (12.3)	100 (21.0)	<0.001
Total hand and wrist	750 (162.0)	785 (140.2)	715 (174.3)	<0.001
Anthropometric measure				
Body mass index	18 (3.1)	17 (2.9)	18 (3.2)	0.004
Height (cm)	144 (18.4)	141 (15.8)	147 (20.2)	0.002
Sitting height (cm)	78 (9.0)	77 (8.0)	79 (9.7)	0.003
Weight (cm)	38 (14.8)	36 (12.5)	41 (16.3)	0.001
Chest circumference (cm)	69 (11.1)	67 (10.1)	71 (11.7)	<0.001
Waist circumference (cm)	61 (9.5)	59 (8.0)	63 (10.3)	<0.001
Hip circumference (cm)	75 (12.1)	74 (11.7)	75 (12.4)	0.236
Shoulder breadth (cm)	31 (4.2)	30 (3.6)	32 (4.6)	0.007
Pelvis width (cm)	23 (3.3)	22 (3.2)	23 (3.3)	0.022

Note. Data denoted as mean (SD); *Mann-Whitney test.

The results of our study indicated that genetic effects were mainly reflected in the bone development of the hand and wrist. Earlier review[5] and a recent study[10] in young children aged 4.5-6.5 years showed that stronger hereditary contributed to the development of bone mass relative to environmental factors such as dietary intake and physical activity.

For the bivariate analysis, Akaike's information criterion (AIC) was used to select the best model for analysis. An AE model showed the lowest AIC (-539.5) compared to ACE (-537.6), CE (-538.1), and AC (-533.6) models. Bivariate Cholesky models were used to partition the phenotypic covariance into A and E components and thus to identify and quantify the contributions of the genetic and environmental background to the total score of skeletal maturity with anthropometric measures. The correlation coefficients with 95% confidence intervals for phenotypic, genetic and environmental effects are presented in Table 3. Moderate genetic correlations were found only for total skeletal maturity vs weight and total skeletal maturity vs waist circumference with r=0.51 and r=0.46, respectively. Our findings indicate that the bone development of the hand and wrist has low correlation with anthropometric measures, suggesting that the anthropometric measures used in this study and the maturation of the bones of the hand and wrist are subject to different genetic and environmental factors.

Table 2. Twin Correlations by Zygosity, and Proportions of Variance Due to Additive Genetic (A), Common Environmental (C) and Specific Environmental (E) Sources of Influence (Age and Sex Adjusted)

Content	Twin Correlations, r (95% CI)		Proportion of Variance, % (95% CI)		
	MZ	DZ	A	C	E
Bones					
Radius	0.49 (0.35-0.59)	0.37 (0.17-0.52)	23 (0-58)	25 (0-52)	51 (41-65)
Metacarpal I	0.76 (0.68-0.82)	0.09 (-0.05-0.23)	73 (60-81)	0 (0-5)	27 (19-40)
Metacarpal III	0.58 (0.45-0.67)	0.28 (0.12-0.43)	57 (21-67)	0 (0-30)	43 (33-55)
Metacarpal V	0.45 (0.31-0.57)	0.38 (0.19-0.53)	14 (0-54)	31 (0-52)	55 (43-68)
Proximal Phalanx I	0.78 (0.7-0.83)	0.21 (0.06-0.36)	76 (65-83)	0 (0-9)	24 (17-33)
Proximal Phalanx III	0.51 (0.38-0.62)	0.21 (0.02-0.38)	50 (17-61)	0 (0-28)	50 (39-63)
Proximal Phalanx V	0.64 (0.53-0.72)	0.28 (0.11-0.44)	64 (35-72)	0 (0-25)	36 (28-47)
Middle Phalanx III	0.57 (0.45-0.67)	0.35 (0.17-0.5)	45 (8-67)	13 (0-44)	43 (33-55)
Middle Phalanx V	0.82 (0.75-0.86)	0.09 (-0.06-0.24)	81 (72-86)	0 (0-5)	19 (14-27)
Distal Phalanx I	0.57 (0.45-0.66)	0.31 (0.11-0.47)	51 (13-66)	5 (0-39)	43 (34-55)
Distal Phalanx III	0.58 (0.46-0.67)	0.19 (-0.01-0.37)	57 (31-66)	0 (0-21)	43 (34-55)
Distal Phalanx V	0.80 (0.73-0.85)	0.12 (-0.02-0.27)	79 (69-85)	0 (0-6)	21 (15-31)
Capitate	0.26 (0.11-0.39)	0.01 (-0.26-0.24)	24 (0-37)	0 (0-27)	76 (63-90)
Hamate	0.38 (0.24-0.5)	0.08 (-0.14-0.29)	36 (5-48)	0 (0-26)	64 (52-78)
Total hand and wrist	0.71 (0.62-0.78)	0.36 (0.18-0.51)	69 (37-78)	2 (0-32)	29 (22-38)
Anthropometric measure					
Body mass index	0.84 (0.8-0.88)	0.46 (0.29-0.6)	76 (50-88)	8 (0-34)	16 (12-20)
Height	0.96 (0.95-0.97)	0.59 (0.45-0.69)	75 (54-97)	21 (0-42)	4 (3-5)
Sitting height	0.94 (0.92-0.95)	0.39 (0.22-0.52)	94 (80-95)	0 (0-14)	6 (5-8)
Weight	0.88 (0.84-0.91)	0.52 (0.36-0.64)	72 (48-90)	16 (0-40)	12 (9-16)
Chest circumference	0.84 (0.79-0.88)	0.50 (0.34-0.63)	68 (44-88)	16 (0-40)	16 (12-21)
Waist circumference	0.83 (0.77-0.87)	0.49 (0.32-0.61)	69 (43-86)	14 (0-39)	17 (13-23)
Hip circumference	0.67 (0.58-0.75)	0.36 (0.18-0.51)	63 (30-75)	5 (0-34)	33 (25-42)
Shoulder breadth	0.81 (0.75-0.86)	0.42 (0.23-0.57)	79 (49-86)	3 (0-32)	19 (14-25)
Pelvis width	0.71 (0.63-0.78)	0.42 (0.23-0.57)	59 (27-78)	12 (0-42)	29 (22-37)

Table 3. Additive Genetic and Environmental Correlations in the Best Fitting Cholesky Model

Trait	Correlations with Total Score, r (95% CI)		
	Phenotypic	A	E
Body mass index	0.07 (-0.05-0.18)	0.16 (0.10-0.40)	0.19 (0.03-0.35)
Height	0.13 (0.02-0.24)	0.09 (0.17-0.35)	0.08 (0.09-0.25)
Sitting height	0.06 (-0.06-0.18)	0.03 (0.25-0.30)	0.09 (0.08-0.26)
Weight	0.20 (0.10-0.30)	0.51 (0.21-0.90)	0.06 (0.11-0.23)
Chest circumference	0.19 (0.09-0.29)	0.17 (0.08-0.41)	0.19 (0.03-0.35)
Waist circumference	0.20 (0.09-0.30)	0.46 (0.15-0.83)	0.04 (0.13-0.21)
Hip circumference	0.24 (0.13-0.34)	0.17 (0.04-0.37)	0.19 (0.02-0.35)
Shoulder breadth	0.21 (0.10-0.31)	0.20 (0.01-0.33)	0.14 (0.03-0.31)
Pelvis width	0.21 (0.10-0.32)	0.24 (0.01-0.47)	0.23 (0.06-0.38)

Note. CI, confidence interval.

In summary, our pilot study indicated that twin correlations of total hand and wrist scores for MZ and DZ twins were 0.71 and 0.36, respectively. Twin correlations for anthropometric measures in MZ pairs were all above 0.71 and even in DZ twins most of them were around 0.50. The bivariate model exhibited moderate genetic correlations only for total skeletal maturity *vs* weight and total skeletal maturity vs waist circumference with r=0.51 (95% CI: 0.21-0.90) and 0.46 (0.15-0.83), respectively. Genetic correlations between other traits and all environmental correlations between traits were <0.30. Genetic factors play important roles in bone development of the hand and wrist in Chinese young twins, however, such genetic effects may differ from those determining anthropometric measures. Our findings should be subject to careful interpretation in the light of small sample size, and further analysis is required in larger studies.

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REFERENCES

1. Zhang A, Sayre JW, Vachon L, et al. Racial differences in growth patterns of children assessed on the basis of bone age. Radiology, 2009; 250, 228-35.
2. PCSC. The standards of skeletal maturity of hand and wrist for Chinese (TY/T001-92). Beijing: Physical Culture and Sports Commission of the PRC, 1992.
3. PCSC. The standards of skeletal maturity of hand and wrist for Chinese-China 05 (TY/T3001-2006). Beijing: Physical Culture and Sports Commission of the PRC, 2006.
4. Tanner J, Healy M, Goldstein H, et al. Assessment of Skeletal Maturity and Prediction of Adult Height (TW3 method). 3rd edition. London: WB Saunders, 2001; 9-22.
5. Pollitzer WS, Anderson JJ. Ethnic and genetic differences in bone mass: a review with a hereditary vs environmental perspective. Am J Clin Nutr, 1989; 50, 1244-59.
6. Li L, Gao W, Yu C, et al. The Chinese National Twin Registry: an update. Twin Res Hum Genet, 2013;16, 86-90.
7. Li L, Gao W, Lv J, et al. Current status of the Chinese National Twin Registry. Twin Res Hum Genet, 2006; 9, 747-52.
8. Gertych A, Zhang A, Sayre J, et al. Bone age assessment of children using a digital hand atlas. Comput Med Imaging and Graph, 2007; 31, 322-31.
9. Becker A, Busjahn A, Faulhaber HD, et al. Twin zygosity. Automated determination with microsatellites. J Reprod Med, 1997;42, 260-6.
10. Willing MC, Torner JC, Burns TL, et al. Gene polymorphisms, bone mineral density and bone mineral content in young children: the Iowa Bone Development Study. Osteoporos Int, 2003;14, 650-8.