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Proximal hip geometry is linked to several chromosomal regions: Genome-wide linkage results from the Framingham Osteoporosis Study

S. Demissie [a], J. Dupuis [a], L.A. Cupples [a], T.J. Beck [b], D.P. Kiel [c], D. Karasik [c,*]

[a] *Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA*
[b] *Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[c] *Hebrew SeniorLife Institute for Aging Research and Harvard Medical School, 1200 Centre Street Boston, MA 02131, USA*

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Abstract

Introduction: Femoral geometry contributes to bone strength and predicts hip fracture risk. The purpose of this study was to evaluate heritability (h^2) of geometric indices of the proximal hip and to perform whole-genome linkage analyses of these traits, adjusted for body size.
Methods: DXA scans of the proximal femur from 1473 members of 323 pedigrees (age range 31–96 years) from the population-based Framingham Osteoporosis Study were obtained. Using the hip structural analysis program, we measured femoral neck length (FNL, cm) and neck-shaft angle (NSA); subperiosteal width (WID, cm), cross-sectional area (CSA, cm^2); and section modulus (Z, cm^3) at the narrowest section of the neck (NN), intertrochanteric (IT) and femoral shaft (S) regions. Linkage analyses were performed for the above indices with a set of 636 markers using variance components maximum likelihood method.
Results: Substantial genetic influences were found for all geometric phenotypes, with h^2 values between 0.28 (NSA) and 0.70 (IT_WID). Adjustment for height and BMI did not alter h^2 of NSA and FNL but decreased h^2 of the cross-sectional indices. We obtained substantial linkage (multipoint LOD >3.0) for S_Z at 2p21 and 21q11 and S_WID at Xq25–q26. Inclusion of height and BMI as covariates resulted in much lower LOD scores for S_Z, whereas linkage signals for S_Z at 4q25, S_CSA at 4q32 and S_CSA and S_Z at 15q21 increased after the adjustment. Linkage of FNL at 1q and 13q, NSA at 2q and NN_WID at 16q did not change after the adjustment.
Conclusion: Suggestive linkages of bone geometric indices were found at 1q, 2p, 4q, 13q, 15q and Xq. The identification of significant linkage regions after adjustment for BMI and height may point to QTLs influencing femoral bone geometry independent of body size.

Keywords: Proximal femur; Geometry; Heritability; Whole-genome linkage; Quantitative trait loci; Body size and body composition

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing an individual to increased risk of fracture [1]. There are over 1.5 million osteoporotic fractures annually in the United States, with hip fracture remaining a leading cause of morbidity and mortality in the elderly that consumes a disproportionate amount of health-care resources and is associated with substantial pain and significantly decreases active life expectancy [2–4]. Also alarming are the predictions of increasing number of fractures and associated health-care burden as the population ages [5]. To advance our understanding of skeletal fragility and improve clinical assessments of fracture risk, knowledge of mechanisms and predictors of hip fractures is greatly needed.

Strength of osteoporotic bones is mainly compromised by age-related changes in the amount and distribution of the calcified tissue within bones. These aspects are quantified by engineers in terms of structural geometry, which determines stresses within bones produced by loading forces. Though low bone mineral density (BMD) has been commonly used as a risk factor for predicting fractures [6], a growing body of

Abbreviations: BMI, body mass index; BMD, bone mineral density; CSA, cross-sectional area; DXA, dual X-ray absorptiometry; FNL, femoral neck length; h^2, heritability; HSA, hip structural analysis; IBD, identical-by-descent; IT, intertrochanteric; NN, narrowest neck; NSA, neck-shaft angle; QTL, quantitative trait locus; S, femoral shaft; VCA, variance component analysis; WID, subperiosteal width; Z, section modulus.

* Corresponding author. Fax: +1 617 363 8936.
E-mail address: karasik@hrca.harvard.edu (D. Karasik).

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evidence indicates that bone geometry also contributes importantly to bone strength and fracture risk [7]. Thus, proximal femora of elderly men and women with any type of osteoporotic fracture have lower estimated bending strength and axial strength, thinner cortices and wider subperiosteal diameters than femora of fracture-free counterparts [8]. Compared to those without fractures, women with hip fractures (as well as their daughters [8,9]) have altered femoral geometry, including wider femoral necks and longer hip axis lengths, independently of femoral neck BMD, age and body size [10–16]. Currently, femoral geometry is assessed non-invasively by radiogrammetry and/or DXA-based hip structural analysis (HSA), as well as by 3D methods like computed tomography [17]. The technique of HSA uses the bone mass data so that genetic influences on mechanical properties might be indirectly evaluated.

There is a great deal of evidence suggesting that osteoporosis has a substantial genetic component [18,19]. While it is well known that BMD is highly heritable [18,19], bone size and architecture are also under strong genetic influence [20]. Both men and women with a maternal history of osteoporosis have been shown to have thinner femoral cortices [21]. So far, there have been relatively few genetic studies on femoral neck cross-sectional geometry in humans, although several genes have been associated with hip geometric traits [22–24]. Genome-wide linkage analyses of femoral geometry using plain radiographs [25,26] and DXA-derived geometric traits [27,28] suggested that the variation of femoral neck geometry is under strong genetic control.

Therefore, to better understand the genetics underlying hip fractures, it is important to examine heritable determinants of bone geometry. The aim of this study was to determine heritability (h^2) of geometric indices of the proximal hip in men and women members of extended pedigrees from the community-based Framingham Osteoporosis Study sample and to perform whole-genome genetic linkage analyses. Additionally, because there are known effects of body size on size and strength of the bones [29] we evaluated whether or not an adjustment for body size would influence the magnitude of heritability and linkage.

Methods

Sample

The sample used for our analyses was derived from two cohorts of the population-based Framingham Heart Study. The Framingham Study Original Cohort began in 1948 with the primary goal of evaluating risk factors for cardiovascular disease. The Original Cohort participants, initially aged 28–62 years, represented two thirds of the households of the Framingham, MA, population and have been examined every 2 years since baseline. In 1971, the Framingham Offspring Cohort Study was initiated with an intent to evaluate the role of genetic factors in the etiology of coronary artery disease and was comprised of 71% of all the eligible adult offspring of couples from the Original Cohort and offspring's spouses. Neither the Framingham Original nor Offspring Cohort was selected on the basis of cardiovascular diseases or osteoporosis. Details and descriptions about the Framingham Osteoporosis Study have been reported [30,31]. The study was approved by the Institutional Review Board for Human Subjects Research of Boston University.

Dual energy X-ray absorptiometry (DXA) and hip structural analysis (HSA)

The participants underwent bone densitometry by DXA with a Lunar DPX-L (Lunar Corp., Madison, WI, USA). The Original Cohort participants underwent bone densitometry during their examination 22 (1992–1993). In order to maximize the sample size, we also used DXA scans from examination 24 (in 1996–1997) for 31 Original Cohort members who did not have DXAs at examination 22. The Offspring Cohort was scanned with the same machine between 1996 and 2001. As described previously [32,33], an interactive computer program (hip structure analysis, HSA) was used to derive a number of structural variables from the femoral DXA scans. The regions assessed were the narrowest width of the femoral neck (NN), which overlaps or is proximal to the standard Lunar femoral neck region; an intertrochanteric (IT) region located along the bisector of the neck-shaft angle (NSA); and the femoral shaft (S)—at distance of 1.5 times the minimum neck width, distal to the intersection of the neck and shaft axes.

HSA provided measures of bone cross-sectional area (CSA, cm^2), section modulus (Z, cm^3) and subperiosteal width (WID, cm) at each of the 3 femoral regions (NN, IT and S). These parameters are measured directly from the mass profiles using a principle first described by Martin and Burr [34]. In addition, the method measures the neck-shaft angle (NSA) and femoral neck length (FNL), defined as distance from the center of femoral head to the intersection of neck and shaft axes (Fig. 1). Note that since the geometry measures are derived from the projected mineral mass, they integrate both trabecular and cortical bone and exclude the non-contributing spaces due to trabecular and cortical pores. An important limitation of the method is that the mineral distribution information incorporated into the section modulus is only relevant to bending in the plane of the scan image.

Together with NSA and FNL, there were 11 phenotypes. Coefficients of variation for the different component variables were previously reported to range from 3.3% (NN_WID) to 9.1% (FNL) [32].

Other measurements

Information on age, sex, weight and height were obtained for each individual at the time of the bone measurement. In brief, in both Cohorts, weight (in pounds) was measured using a standardized balance beam scale. Height (without shoes) was measured to the nearest 1/4 in. using a stadiometer. Body mass index (BMI) was then calculated in kg/m^2.

Genotyping

A genome scan was performed in the Framingham Heart Study in two steps. In the first phase, 1702 individuals in the largest 330 families were genotyped without regard to their clinical characteristics, using 422 polymorphic markers (markers set 9, average heterozygosity 0.77; sex-averaged mean inter-marker spacing of 8.6 cM, NHLBI Mammalian Genotyping Service in Marshfield, WI [35]). In the second phase, an additional 184 members of the 330 largest pedigrees were genotyped on 382 markers (markers set 13, average heterozygosity 0.76; sex-averaged mean inter-marker spacing of 8.9 cM). There were 262 markers in common with marker set 9. Also, ninety-four additional markers genotyped on these 330 largest pedigrees, used to augment the original genome scan, were available to us and included in the linkage analyses. A total of 636 markers, including 21 markers on chromosome X, were thus studied, with an average marker spacing of 5.7 cM. Genotype data cleaning, including verification of family relationships and Mendelian inconsistencies, have been previously described [36].

Finally, members of the 323 families with family sizes ranging from 2 to 30 genotyped individuals contributed to the linkage analyses (with 66% of the sample representing individuals in pedigrees with 2 to 6 person). Out of a total of 1702 genotyped Framingham participants, 1473 had HSA measurements. There were 390 members of the Original Framingham cohort and 1083 participants from the Offspring Cohort. The sample with genotyping and bone geometric phenotypes included the following relative pairs: 678 parent-offspring pairs, 1074 sibling pairs, 659 cousin pairs and 380 avuncular pairs.