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Genetic determinants of osteoporosis susceptibility in a female Ashkenazi Jewish population

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Purpose: To determine the heritability of low bone mineral density (BMD) at the hip in Ashkenazi Jewish families. **Methods:** BMD at hip was accessed by dual x-ray absorptiometry (DEXA) in 166 female subjects from 61 families. Variance component analysis was used to estimate genetic contributions. **Results:** We observed significant genetic contributions to age-adjusted BMD at the femoral neck as measured by heritability 0.67 ($P < 0.0001$). **Conclusion:** There is significant genetic determination in decreased BMD at the femoral neck in an Ashkenazi Jewish female population. These results warrant further gene mapping studies in this population to identify osteoporosis susceptibility loci. ***Genet Med* 2004:6(1):33–37.**

Key Words: *osteoporosis, bone mineral density, genetics, heritability, familial correlation*

Osteoporosis is a prevalent health problem that causes considerable morbidity and mortality. Presently, it is estimated that 10 million American women have osteoporosis and 18 million have low bone mass.[1–3] This number is expected to increase at the rate of 2% per year well into the 21st century.[3] In the United States, more than 1.3 million osteoporotic fractures occur yearly with an estimated direct cost of 13.8 billion dollars.[2–4] Although multiple environmental factors influence the development of osteoporosis, it is clear that the major determinant for the disease is oligogenetic control of the achievement of peak bone mass.[5–15] Several twin studies have concluded that up to 85% of the variance in bone mineral density (BMD) in axial and appendicular skeleton is accounted for by genetic factors.[6–11] In one of the largest studies, 85% and 81% of the BMD variation at the spine and hip, respectively, was attributed to heredity alone.[10] The identification of genes that increase susceptibility to low BMD has significant diagnostic and therapeutic implications.

To identify loci that determine susceptibility to osteoporosis, we initiated a study of a single ethnic group, Ashkenazi Jews, where the incidence of osteoporosis is known to be high (7.3%).[16] Familial aggregation of osteoporosis in this ethnic group was previously reported with 45% of cases having a positive family history.[17] In this latter study, the empiric risk of developing clinical osteoporosis was 33% for a mother and 19% for a sister of a proband. In this present study, our aim was to estimate the heritability of low BMD at the hip in osteoporosis families of Ashkenazi Jewish descent. The observed result, a significant heritability of BMD in the Ashkenazi Jewish families, increases the probability of identifying osteoporosis susceptibility genes in this population.

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MATERIALS AND METHODS

Subjects

To minimize the variation in bone mass inherent between men and women,[18–20] only female subjects were studied. Subjects comprised 166 Ashkenazi Jewish (AJ) females from 61 independent families. Among these subjects, 106 were from the proband generation, 50 from the offspring generation, and 10 from the parental generation. There were 61 Jewish probands, age 37 to 89 years (mean 61 years).

Subjects were recruited by the General Clinical Research Center staff after a proband was identified by a participating physician at Cedars-Sinai Medical Center. Institutional Review Board approval was obtained. Written informed consent was obtained by a physician investigator, and each participant was assigned a code number. Subjects were women $>$ 20 years of age. Probands were individuals with osteoporosis defined as (1) a BMD $>$ 2.5 standard deviations (SD) below an idealized young adult mean or T score > -2.5 by dual x-ray absorptiometry (DEXA) or (2) presence of low trauma fracture. Exclusionary criteria included vitamin D deficiency or intoxication, primary hyperparathyroidism, hyperthyroidism or untreated hypothyroidism, renal insufficiency, and current or previous prolonged exposure to immunosuppressive agents.

Measurements

All subjects underwent the clinical, biochemical, and densitometry assessment in the study. Information on smoking status, alcohol consumption, estrogen use, height, and weight was also collected.

Densitometry

BMD at the left femoral neck was measured by DEXA on a QDR-2000 (Hologic, Inc., Waltham, MA) or a DPX-L densitometer (Lunar Corp., Madison, WI). The results were expressed as T and Z scores. The T score is a measure of deviation from the expected population mean of peak young adult bone mass. Clinically, it is used to predict fracture risk. The Z score is the measure of deviation from the expected population mean of age-matched referent population. All DEXA data were expressed as the mean ± standard deviation (SD).

Biochemical

For each subject, blood samples (90 mL) and a > 2-hour fasting, postfirst void urine was collected. Biochemical analyses included serum measurement of creatinine, calcium, albumin, magnesium, alkaline phosphatase, thyroid-stimulating hormone, and urine measurement of calcium and creatinine, by automated methods. Serum 25-hydroxyvitamin D, iPTH, osteocalcin, bone-specific alkaline phosphatase, and urine N-telopeptide levels were also determined.[21] All samples from a single pedigree were assayed together to avoid interassay variation. All information, samples, and data were identified by a code number; laboratory investigators were blinded to phenotypic status.

Statistical analysis

Adjustment of BMD-related traits

In order to assess the genetic influence of BMD, we adjusted BMD by nongenetic risk factors that may influence BMD, including age, body mass index [BMI, weight (Kg) divided by the squares of height (M)], smoking status, alcohol consumption, estrogen usage, and measured biochemical variables. Because there were correlations between subjects within a family, generalized estimating equations (GEEs) with GENMOD were used to analyze these data for both univariate and multivariate analysis (SAS/STAT User's Guide, 1990).[22] We calculated the univariate correlation between BMD and each variable mentioned above. All variables that showed association at a 0.1 significance level in the univariate analysis were included in the multivariate analysis. The variables remaining in the final model were based on the model's comparisons using the likelihood ratio test. The analyses were performed separately for femoral neck T and Z scores (age was not adjusted for Z score since it was an age-adjusted value already). The residual values were obtained after the associated variables were taken into account. Such residual values (adjusted BMD) were used in the familial correlation estimation.

Familial correlation and heritability estimation

Familial correlations of adjusted bone density traits (using residual values, see "Adjustment of BMD-related traits") were calculated using the FCOR (Familial Correlation program of S.A.G.E. [Statistical Analysis for Genetic Epidemiology]).[23] Familial correlations were used to evaluate the familial aggregation of the quantitative traits. It was assumed that the correlation in blood relatives was higher than that of the random sample (i.e., equal to 0) if the trait is determined by familial factors (including genetic and shared environmental factors). We calculated the correlations of mother-daughter pairs and sister-sister pairs by each of three weighting methods (equal weight to pairs, equal weight to pedigrees and equal weight to nuclear families). The *t* test was used to assess whether these correlations were significantly greater than zero.

To assess the relative contribution of genetic and environmental factors to bone density and to the development of osteoporosis, we estimated the heritability (h^2) for each trait using variance component analysis as incorporated in the SOLAR software (Sequential Oligogenic linkage Analysis Routines).[24] The h^2 was defined as the ratio of genetic variance (s_g^2) over total phenotypic variance (s_p^2). The phenotypic variance may be due to genetic variance and shared or nonshared environmental variance. We calculated the variance components using the kinship matrix formulas using the observed maximum likelihood parameter estimates of the polygenic model. All variables significantly associated with BMD in the final model (see "Adjustment of BMD-related traits") were included as covariates in the model to estimate the h^2. The likelihood ratio test was used to test the null hypothesis of no genetic determination: $h^2 = 0$.

RESULTS

There were 61 independent Jewish families with a total of 166 female subjects in our sample. Most families (78.7%) had 2 to 4 individuals. Eighty seven (52.4%) subjects were the first-degree relatives of probands. The average age of all study subjects was 54.3 years, ranging from 21 to 89 years. Table 1 shows the distribution of potential risk factors for osteoporosis among probands, first-degree relatives, and other relatives.

Factors influencing the BMD in Jewish families

Using univariate analysis, age, BMI, smoking, drinking, estrogen use, and serum measurement of albumin and magnesium were each significantly associated with femoral neck BMD T-scores, whereas only BMI was significantly associated with age-adjusted femoral neck BMD Z-scores. After all these significant variables were included in the multivariate analysis, only age ($P < 0.0001$), BMI ($P < 0.0001$), and albumin ($P = 0.055$) remained statistically significant for femoral neck BMD T-scores. Therefore only age, BMI, and albumin were used as covariates for femoral neck BMD T-scores in the later analyses.

Familial correlation

Table 2 shows the familial correlation of the adjusted BMD traits in these Jewish families. Because three different weighting methods gave similar results, the results from equal pairs are summarized in Table 2. The correlation of femoral neck (both T score and Z score) between sister-sister pairs were significantly greater than the null hypothesis ($r = 0$) (all $r \geq 0.36$, all $P < 0.01$).

Heritability estimation

Table 3 shows the upperbound heritability estimates of each trait in these Jewish families. The heritability estimates for the

Table 1
Risk factor distribution in proband and relatives[a]

Factors	Proband ($N = 61$)	First-degree relatives ($N = 87$)	Other relatives ($N = 18$)
Age	61.0 (±10.7)	49.0 (±13.8)	57.4 (±17.0)
BMI	22.5 (±3.0)	23.9 (±4.5)	25.5 (±5.8)
Smoking	0%	9.2%	5.6%
Drinking	36.1%	32.2%	11.1%
Estrogen use	46.2%	30.0%	40.4%
Serum biochemistries			
Calcium	9.1 (±0.4)	9.0 (±0.4)	9.0 (±0.3)
25-hydroxyvitamin D	27.8 (±7.3)	26.5 (±9.7)	23.1 (±7.7)
iPTH	24.0 (10, 69)	28.0 (10, 123)	26.5 (10, 50)
Creatinine	0.6 (0.4, 1)	0.6 (0.4, 1.3)	0.6 (0.4, 0.7)
Osteocalcin	4.8 (1.6, 14)	6.7 (1.4, 23)	4.2 (1.4, 14)
Bone-specific alkaline phosphatase	7.9 (2, 15)	8.2 (4.1, 22)	9.3 (4.5, 17)
Thyroid stimulating hormone	1.30 (0.02, 4.10)	1.20 (0.02, 7.90)	1.65 (0.67, 3.80)
Albumin	4.4 (3.8, 4.9)	4.5 (3.5, 5.0)	4.2 (3.9, 4.9)
Magnesium	2.2 (1.7, 2.8)	2.1 (1.8, 2.8)	2.1 (1.7, 2.5)
Urine biochemistries			
Calcium	5.7 (0.5, 30.2)	6.0 (0.6, 49.2)	9.6 (1.0, 24.4)
Creatinine	54 (9, 178)	86 (15, 283)	86 (17, 206)
N-telopeptide	24 (8, 94)	31 (9, 109)	34 (17, 74)
BMD trait by DEXA[b]			
Femoral neck T score	−2.31 (±0.76)	−1.44 (±1.05)	−1.65 (±1.00)
Femoral neck Z score	−0.93 (±0.64)	−0.60 (±0.88)	−0.35 (±0.84)

[a]For quantitative traits with a normal distribution, we calculated the mean (±SD); for those traits nonnormally distributed, we state the median and range (minimum, maximum) values.
[b]Dual energy x-ray absorptiometry (DEXA) score normalized to a normative population at peak bone mass (T score) and in same decade of life (Z score).

Table 2
Familial correlations for adjusted bone mineral density (BMD) traits according to equal pairs analysis

BMD trait by DEXA[a]	Mother-Daughter Paris ($N = 54$) correlation (SE)	Sister-Sister Pairs ($N = 64$) correlation (SE)
Femoral neck T	0.37 (0.14)[b]	0.37 (0.12)[b]
Femoral neck Z	0.33 (0.14)[b]	0.36 (0.12)[b]

[a]Dual energy x-ray absorptiometry (DEXA) score normalized to controls at peak bone mass (T score) and in same decade of life (Z score).
[b]$P < 0.01$.

Table 3
Heritability estimates for bone mineral density (BMD) in Ashkenazi Jewish families

BMD trait by DEXA[a]	Heritability (SE)	Covariates	*P* value
Femoral neck T	0.73 (0.19)	age, BMI, albumin	<0.001
Femoral neck Z	0.67 (0.20)	BMI	<0.001

[a]Dual energy x-ray absorptiometry (DEXA) score normalized to controls at peak bone mass (T score) and in same decade of life (Z score).

left femoral neck T and Z DEXA scores were 0.73 and 0.67, respectively, and highly significant (both $P < 0.001$).

DISCUSSION

We conducted a study of females of Ashkenazi Jewish ancestry to assess the genetic determination of osteoporosis susceptibility in this population. After taking into account a large number of potential risk factors influencing BMD, we observed significant familial resemblance among females within the family and obtained highly significant heritability estimates of BMD. The results demonstrate a strong genetic component ($h^2 = 0.67 \sim 0.73$) to the determination of BMD of the hip, specifically at the femoral neck in this ethnic group.

Familial resemblance might be due to genes or to shared environmental factors within families.[25] Although some common environmental factors may be responsible for the familial resemblance, such as smoking status, alcohol consumption,

estrogen usage, we found no association between these factors and BMD. After adjusting for the previously stated potential risk factors, our estimate of correlation between mothers and daughters was 0.33 for the femoral neck, a finding that is consistent with the findings in studies of healthy[12] and osteoporotic[26] mothers and their daughters. The sister-sister correlation we observed was higher than a recent study, in which Baudoin et al.[25] reported a correlation of 0.16 among sibs for femoral neck.

The estimates of heritability for BMD are relatively high in most twin studies ($h^2 > 0.8$). The assumption in twin studies is that the degree to which monozygotic (MZ) twins share a common environment is the same as that for dizygotic (DZ) twins. This is rarely the case and often leads to overestimates of heritability.[27] Our h^2 estimates of 0.73 and 0.67 for the femoral neck T and Z scores, respectively, fall in the middle range of h^2 estimates obtained from twin studies.[7–10,12] In addition, two family studies reported the heritability of BMD in Caucasian populations that were lower than that reported from the twin studies. Danielson et al.[28] found the heritability estimates ranged from 0.50 to 0.63, whereas Deng and his colleagues[29] estimated that heritability at the hip was 0.65. Although our h^2 seems to be greater than those previously reported h^2 from family studies, such difference may not be statistically significant. In general, the majority of heritability estimates for BMD are in the range of 0.60 to 0.70, which is at the higher end for various common complex traits.

The limitations of our study should be noted. Although the bias of common familial environmental effects has been reported as being small,[30] it is noteworthy that our data were obtained from a single ethnic group among whom cultural background and environmental conditions were generally similar so that the observed heritability may be overestimated. In addition, our sample size is still modest. The impact of dietary differences and exercise on BMD was also not accounted for in our study. Two studies, a female twin study by Slemenda et al.[10] and a male-female family study by Baudoin et al.,[25] evaluated the genetic and environmental effects on BMD by comparing the results before and after adjustment for environmental factors including dietary calcium intake and physical activity. The female twin study of Slemenda[10] is the more informative of the two, demonstrating increased heritability estimates for hip BMD after the adjustment for environmental factors. The smaller male-female family study of Baudoin[25] in the general French population showed that adjustment for environmental factors did not change the significant interclass correlations in femoral neck BMD among the families of male probands. In that study, a significant interclass correlation in femoral neck BMD was uncovered between the children of female probands and a previously significant interclass variation between the proband and their siblings was lost after adjustment for environment. Thus, unmeasured dietary and physical activities in our samples may not have had significant effect on the estimate of heritability of BMD. The accuracy of BMD as measured by DEXA in predicting the risk of osteoporotic fractures also warrants caution. It is important to recognize that fracture risk is multifactorial. The likelihood of a fracture depends on bone strength as well as the forces applied.[31] Diminished bone strength is composed of abnormalities of bone quantity (mass, mineral density, and size) and quality (macro- and microarchitecture, bone turnover, material properties such as microdamage, and collagen cross-linking).[32] Furthermore, genes regulating bone structure may differ than those regulating BMD.[33]

Osteoporosis is an oligogenic disease and BMD is a complex trait.[34] It is presumed that multiple genes contribute to the variation in BMD. Genome-wide linkage screens conducted in humans and animals have reported linkage of femoral neck and lumbar spine BMD to chromosomes 1p, 2p, 4q, 5q, 6p, 11q, 13q, and 22q.[35–38] Our study is the first to describe the heritability of low BMD in Ashkenazi Jewish females. The relative homogeneity and the high estimates of heritability of BMD present in this population, particularly at the femoral neck, may prove valuable for the identification of site-specific osteoporosis susceptibility loci in future linkage and gene mapping studies.

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