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Farnesyl Diphosphate Synthase: A Novel Genotype Association with Bone Mineral Density in Elderly Women

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Abstract

Mini-Abstract—Farnesyl diphosphate synthase (FDPS) is the molecular target of nitrogen-containing bisphosphonates. We analyzed the association between a SNP in the FDPS gene with bone mineral density (BMD) in post-menopausal Caucasian women. The SNP was associated with decreased BMD after adjusting for age and BMI. Genetic variation in FDPS may contribute to BMD in this population.

Objective— We evaluated the association between a single nucleotide polymorphism in the farnesyl diphosphate synthase gene (FDPS), BMD and bone turnover markers.

Methods— 283 community-dwelling Caucasian women aged 65 or older were screened from the greater Boston area. A validated FDPS SNP (*rs2297480*, *A/C*) was genotyped and evaluated for effect on bone mineral density (spine, hip, forearm) and bone turnover markers (urine N-telopeptide cross-linked collagen type 1, osteocalcin and bone-specific alkaline phosphatase).

Results— BMD was lower at all sites measured in women with the C/C or C/A genotypes. Statistically significant differences ($p<0.05$) were found at the PA spine, trochanter, distal radius, and proximal ulna after adjustment for age and BMI. No significant differences were found in bone turnover markers.

Conclusion— These findings suggest that a single nucleotide polymorphism in the FDPS gene (*rs2297480*) may be a genetic marker for lower BMD in postmenopausal Caucasian women.

Key Terms

bone mineral density; farnesyl diphosphate synthase; genetic association; osteoporosis; polymorphism

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Introduction

Osteoporosis is associated with increased morbidity and mortality. The National Osteoporosis Federation estimates 10 million Americans over the age of 50 have osteoporosis and an additional 34 million have low bone mass [1]. Forty percent of postmenopausal women are estimated to have an osteoporotic fracture over their lifetime [2]. The treatment of osteoporosis and resulting fractures costs $18 billion annually in the United States [3]. Although many advances have been made in therapeutic interventions, osteoporosis remains a highly prevalent disease in the postmenopausal population.

Family history is a major risk factor for osteoporosis [4]. Several twin and family studies suggest that heritability strongly contributes to BMD [5–7] and osteoporotic fracture risk [8–10]. Genetic factors also play a role in expression of biochemical markers of bone turnover, skeletal geometry and ultrasound properties of bone [11–14]. These observations led to interest in finding genes that predispose individuals in the general population to osteoporosis. Association studies have begun to identify potential susceptibility genes for osteoporosis [15].

Bisphosphonates are potent inhibitors of osteoclasts which reduce bone turnover, increase bone mass, and improve bone mineralization [16]. Although this class of compounds has been known for decades, only recently has its biochemical mechanism of action been explained. Nitrogen-containing bisphosphonates inhibit farnesyl diphosphate synthase (FDPS), a key enzyme in the mevalonate pathway (17). Through this mechanism, bisphosphonates inhibit prenylation and sterol synthesis in osteoclasts and induce osteoclast apoptosis [17]. However, the activity of farnesyl disphosphate synthase might impact bone mass in women who are not on therapy by alterations in osteoclast activity. Furthermore, genetic polymorphisms within the FDPS gene may contribute to bone density and turnover in addition to the response to bisphosphonates. In the present study, we examined the association of two common validated polymorphisms in the human FDPS gene (dbSNP: *rs2297480; rs10796941*) with bone mass in postmenopausal women.

Materials and Methods

Study Population

573 community-dwelling women aged 65 or older were screened from the greater Boston area for a single-center clinical trial as previously reported [19]. Participants were excluded if they had a history of illnesses that could affect bone mineralization or calcium metabolism. After screening, 373 women were enrolled for a clinical trial. Blood samples were obtained from 300 of the 373 randomized subjects. Of these, 283 were Caucasian and included in our analyses for homogeneity. This protocol was approved by the institutional review board at the Beth Israel Deaconess Medical Center in Boston, MA. Participants were advised of the nature of the initial study and provided written informed consent prior to participation including consent for genotyping.

Clinical Examination

Bone mineral density of the hip (total hip, femoral neck, trochanter, and intertrochanter), lumbar spine (posteroanterior and lateral), and radius and ulna (ultra-distal, mid-third, and one-third distal) were measured by dual-energy X-ray absorptiometry ([DXA] QDR 4500A densitometer; Hologic, Inc, Bedford, Mass). The coefficients of variation of BMD in elderly women (mean [SD] age, 71 [7] years) for the densitometer used were 1.7% for the lumbar spine, 1.2% for total hip, and 1.9% for femoral neck [20–21]. Quality control for bone density scans was performed by Synarc, Inc (San Francisco, Calif).

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A marker of bone resorption, urine N-telopeptide cross-linked collagen type 1 (NTx), was assessed with an ELISA (Osteomark7, Ostex International, Inc., Seattle, WA; nmol/liter of bone collagen equivalents/creatinine, intraassay CV 5–19%). Urine for NTx assessment was collected upon second void at 0600–0800 h after an overnight fast and was frozen at −20 C. Serum tests for bone formation were intact osteocalcin (Novocalcin, Quidel Corp., Mountain View, CA; ng/ml, intraassay CV 4.8–10.0%) and bone-specific alkaline phosphatase (BSAP) (Alkphase-B, Quidel; U/liter, intraassay CV, 3.9–5.8%). Serum 25-hydroxyvitamin D was measured by radioimmunoassay (DiaSorin, Stillwater, MN; ng/ml, intraassay CV 10.8%). PTH was measured by allegro immunoradiometric assay (Nichols Allegro, San Juan Capistrano, CA; pg/ml, intraassay CV 1.8–3.4%). Serum was drawn after an overnight fast and stored at −80 C. All assays were simultaneously run at the end of the study by a single laboratory technician. Additional serum measurements included calcium, albumin, and phosphate.

Genotyping

DNA was isolated from frozen buffy coats by standard methods (22). PCR reactions were performed in a total reaction volume of 50ul. PCR reaction mixtures consisted of 50ng DNA, 1.5mM $MgCl_2$, 1X NH_4^+ buffer, 200uM dNTPs, 1.5U Taq DNA polymerase, distilled H_2O, and 0.6uM of primers. Amplifiction of rs2297480 used forward primer 5′-AGGAATCCGTATCTGGGAAC-3′ and reverse primer 5′-CAACTCTAGACACCCCCAGAAG-3′ and genotypes assigned by fluorescence polarization [18]. Amplification of *rs1079641* used primers 5′-ACTACAGGAGCGAGCCTCTA-3′ and 5′ R-AGGTGGAAGGATCGCTTGAG-3′. PCR cycling conditions included an initiated 5 minute step at 95°C followed by 34 cycles of denaturing at 95°C for 30s, annealing at 63°C for 15s, and extension at 72°C for 30s. For genotyping, 15ul of each PCR product was digested with 5 units of *NlaIII* enzyme overnight and fragments resolved on 3% agarose gel for 4 hours at 100 volts and visualized in the presence of ethidium bromide. Genotypes were assigned by direct comparison to sequence verified control samples run in parallel.

Statistical Analyses

Baseline data are summarized as means and standard deviations. Hardy-Weinberg equilibrium was tested using a Chi-square test. We estimated least-square means and their associated standard error after adjusting for age and BMI, since these factors are known to effect bone mineral density for two potential models: once comparing results across the three SNP genotypes, once comparing results between the common homozygote (AA) with the rarer homozygotes (CC) and heterozygotes combined because of the small number of the less common homozygote.

Results

Of the two SNPs tested in this study, *rs10796941* is located in intron 3 of the FDPS gene while *rs2297048* is located in the promoter of FDPS at position −99 upstream of the translation start site. Because these two SNPs were found to be in complete linkage equilibrium in this sample, only the results of the −99 promoter polymorphism are presented. Among subjects with complete data, one hundred forty-eight (52.3%) women had the AA genotype, one hundred twenty-one (42.8%) had the CA genotype, and fourteen (4.9%) had the CC genotype. The distribution was in accordance with Hardy-Weinberg equilibrium ($p>0.2$). Because of the small number of subjects with CC genotypes, we examined the effect of the C allele by combining the CC and CA genotypes.

Clinical characteristics of the study population are shown in Table 1. The mean age of the women was 71±5 years and the mean body mass index (BMI) was 27±6 kg/m^2. There were no differences in height, weight, dietary calcium or vitamin D intake, levels of serum calcium,

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parathyroid hormone or 25 hydroxyvitamin D between women with or without one or more C alleles. There were no differences in the markers of bone turnover between these 2 groups.

At the PA spine, trochanter, radius and ulna, the presence of a C allele contributed to significant reductions in bone mineral density. After adjustment for age and BMI, the C allele continued to be associated with a diminished BMD at most sites (Table 2). For example, the presence of a C allele was associated with 0.045 g/cm^2 lower bone mineral density at the PA lumbar spine.

We also examined each genotype separately (Table 3). The majority of skeletal sites showed the lowest bone mineral densities with the CC and CA genotypes and the highest BMD with the AA genotype. Of these, the PA lumbar spine, trochanter, and proximal ulna reached statistical significance ($p<0.05$) and all other sites except the lateral lumbar spine trended towards significance. After adjustment for age and BMI, only the proximal ulna achieved statistical significance.

Discussion

This study is the first to examine the association of a common polymorphism in the FDPS gene with bone mineral density and bone turnover markers. We found that postmenopausal women with a CC or CA genotype at the polymorphic promoter site had lower BMD at most skeletal sites compared to the AA genotype. The most pronounced effect was at the PA spine, trochanter, and proximal ulna. These findings were significant after adjustment for age and BMI. Bone turnover markers did not show significant associations with the FDPS genotype.

Farnesyl diphosphate synthase, a key branch point enzyme in the mevalonate pathway, is the molecular target for nitrogen-containing bisphosphonates [17,23–25]. Nitrogen-containing bisphosphonates inhibit FDPS and prevent post-translational prenylation of small GTPases such as Ras, Rho, and Rac [26]. These GTPases are important signaling proteins in osteoclast maintenance including cell morphology, membrane ruffling, trafficking of endosomes, and cell survival. The lipid prenyl group anchors these proteins in cell membranes and is required for their function [27–30].

The functional consequences of the FDPS C/A polymorphism (*rs2297480*) have not been established. In silico analysis of this polymorphism using the program FastSNP (http://fastsnp.ibms.sinica.edu.tw) reveals that the A allele may create a binding site for Runx1 (AML1/Cbfa1), a transcription factor essential for hematopoiesis [31]. Runx factors recruit co-regulatory proteins important for signal transduction mediation [32]. Real-time PCR has identified Runx1 as the predominant member of the Runx family in mouse osteoclast and osteoclast-precursor cells [33]. Interestingly, Runx1 mRNA expression decreases with the addition of NF-kB ligand (RANKL), the major stimulator of osteoclast differentiation and activity, in these mouse models [33]. By binding to the FDPS promoter site made by the *rs2297480* A allele, Runx1 may decrease osteoclast activity by inhibiting FDPS transcription. Further *in vitro* studies are necessary to show the level of transcription inhibition caused by each *rs2297480 C* to A allele change.

The molecular mechanisms that explain the differences in BMD but not bone turnover markers are unclear. A mechanistic explanation for our findings may include timing of the polymorphism effect. BMD in women is determined by peak bone accrual in adolescence and early adulthood with postmenopausal bone loss. At least 90% of peak bone mass is acquired by age 18 [34]. The FDPS SNP studied may influence the expression of the FDPS gene and enzyme levels during this period of bone accrual. The CC genotype and/or the C allele may confer higher osteoclast activity during this period and cause a higher bone resorption rate and a lower peak BMD. Alternatively, the major defect caused by FDPS genetic variation may occur after menopause. A longitudinal study is needed to assess these hypotheses.

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This study has several strengths and limitations. Participants in the study were community-dwelling women 65 years or older studied at a single center in Boston, MA. Our analysis focused on Caucasian women for greater genetic homogeneity. Thus, the findings may not generalize to other populations at risk for osteoporosis. Population stratification can promote false-positive results and non-reproducible findings [35]. Our study is the first to examine a genetic polymorphism in farnesyl diphosphate synthase, the target of inhibition by nitrogen-containing bisphosphonates and an important enzyme for osteoclast activity. However, we also only looked at two SNPs in the FDPS gene. Other SNPs may have contributed to our results.

In summary, our findings suggest that genetic variation in the farnesyl diphosphate synthase gene is associated with bone mineral density in postmenopausal elderly women and may have a novel role in the development of osteoporosis. These findings require confirmation with larger cohorts, different populations and multiple FDPS SNPs.

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TABLE 1

Baseline Characteristics

	FDPS Genotype		
Variable (SD)	**AA (n=148)**	**CA (n=121) and CC (n=14)**	**p-value**
Age, yrs	71.06 (5.04)	71.65 (5.57)	0.412
Height, cm	158.91 (6.33)	158.59 (6.48)	0.907
Weight, kg	69.16 (16.58)	67.64 (13.72)	0.629
BMI, kg/m^2	27.38 (6.26)	26.85 (4.93)	0.799
Dietary calcium, mg/d	905.88 (428.30)	861.42 (426.88)	0.403
Dietary vitamin D, IU/d	247.00 (201.09)	235.73 (161.34)	0.870
Serum calcium, mg/dL	8.84 (0.36)	8.91 (0.39)	0.122
Serum albumin, g/dL	4.24 (0.25)	4.24 (0.28)	0.904
Serum 25-hydroxyvitamin D, ng/mL	18.23 (8.00)	19.47 (9.06)	0.337
Serum PTH, g/dL	35.94 (13.46)	36.78 (18.11)	0.960
Urinary NTx, nmol/BCE·mmol creatinine	334.51 (276.64)	376.82 (340.61)	0.208
BSAP, U/Liter	23.57 (7.20)	25.30 (8.28)	0.104
Osteocalcin, ng/mL	9.43 (3.77)	10.31 (5.09)	0.201
Serum total cholesterol	227.03 (36.34)	219.05 (34.73)	0.055

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TABLE 2

Bone Mineral Density at Baseline (Adjusted for Age and BMI), by Allele (No order)*

Site	No C Allele, g/cm^2 [AA] (n=148)	Any C Allele, g/cm^2 [CC and CA] (n=135)	p-value
PA spine	0.904 (0.013)	0.860 (0.014)	0.020
Total Hip	0.799 (0.009)	0.774 (0.010)	0.067
Femoral Neck	0.658 (0.007)	0.640 (0.007)	0.081
Trochanter	0.612 (0.008)	0.588 (0.008)	0.039
Distal Radius	0.351 (0.005)	0.335 (0.005)	0.030
Proximal Ulna	0.544 (0.005)	0.524 (0.006)	0.011

*Results as predicted mean, g/cm^2 (Standard error of the mean)

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TABLE 3

Bone Mineral Density at Baseline (Adjusted for age and BMI), by Genotype*

Site	AA Genotype, g/cm^2 (n=148)	CA Genotype, g/cm^2 (n=121)	CC Genotype, g/cm^2 (n=14)	p-value (Across all genotypes)
PA spine	0.904 (0.013)	0.859 (0.014)	0.861 (0.048)	0.066
Total Hip	0.799 (0.009)	0.776 (0.010)	0.763 (0.030)	0.173
Femoral Neck	0.658 (0.007)	0.640 (0.008)	0.636 (0.023)	0.215
Trochanter	0.612 (0.008)	0.590 (0.009)	0.568 (0.026)	0.088
Distal Radius	0.351 (0.005)	0.334 (0.006)	0.341 (0.017)	0.089
Proximal Ulna	0.544 (0.006)	0.524 (0.006)	0.520 (0.018)	0.038

*Results as predicted mean, g/cm^2 (Standard error of the mean)