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Autosomal dominant high bone mass: The phenotype. A brief description

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In the course of genetic studies, we encountered a kindred with an autosomal dominant mutation resulting in a phenotype (high bone mass, HBM mutation) characterized by a marked increase in peak BMD[1,2]. The phenotype was caused by a missense mutation resulting in a G171V substitution in Lrp-5[2]. This report includes a description of the phenotype in affected individuals, and examines the phenotype in this kindred. This discovery offers interesting information about the function of genetic regulation of peak bone mass in humans. Polymorphisms in this gene may be responsible for some of the variation in BMD in the population at large[3].

The 18-year-old proband was referred by her orthopedist to the Creighton Osteoporosis Research Center (ORC) in 1995 for evaluation of "unusually dense bones". The physical exam revealed excellent health. Radiographs of the entire skeleton on visual inspection revealed somewhat dense bones with thickened cortices. All bones of the skeleton were normally shaped. DXA examination of the mother, father and a male sib suggested that the proband inherited a high bone mass (HBM) trait from her mother. We identified and phenotyped 37 members of the kindred (three were phenotyped ante mortem) who were informative for study of linkage. The Creighton University Institutional Review Board approved the study. Each subject gave signed consent prior to participating in the project.

The kindred was of mixed Caucasian (European) descent, largely English, having settled in the central plains, principally South Dakota. The pattern of inheritance of the HBM trait in this family is autosomal dominant. Clinical history did not reveal awareness of anything unusual about the skeletal health of any of the affected or unaffected members of the kindred. None of the affected members of the kindred was aware that the skeleton was particularly massive. However, some clinical features are interesting. For example, none of the 21 affected persons (17 adults and 4 children) who ranged in age from 3 to 86 years had ever been known to suffer a fracture (one suffered a radial epiphyseal dislocation in childhood). Two affected persons described considerable trauma associated with wisdom tooth extractions. Total hip replacement performed because of coxarthrosis in two affected subjects resulted in unexpectedly prolonged (11 hours in one case) and difficult operations. The surgeons commented about the apparent density of the femur, but did not pursue the issue further.

Skeletal radiographs showed no abnormalities, and do not hint that the spine in each case is about 5 standard deviations above average. There were no skeletal radiographic lesions diagnostic of known syndromes of increased bone density.

All of the serum calcium and phosphorus concentrations were within the normal reference range for children and adults. All of the values for osteocalcin (OC) were within the normal range for adults (<41.0 ng/mL). One of the OC values in affected children (142.3 ng/mL), and two in unaffected children (134.7 and 128.1 ng/mL) were above the highest value for the normal age-specific reference range (123.0 ng/mL). Red and white blood cell counts were within the normal reference range in all members of the kindred in whom they were available (N=19).

A transilial biopsy was performed on a 57-year-old affected male member of the kindred. The cortices and trabeculae both appeared thickened. Trabecular bone volume was 33.9% (14-30) The tetracycline-based remodeling dynamics were normal.

Among the adult female members of the kindred (mean values) spine BMC was about 80% greater, and BMD about 50% greater in the affected individuals and about 5 standard deviations greater than reference normals. Importantly, the

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spine area was about 15.5% greater in the affecteds. Findings in the hip were similar, although the BMC was 67% and BMD was 56% greater in the affecteds, and about 3.35 standard deviations greater than reference normals. Hip area was larger in the affecteds by about 7.0%. The total body BMC was 68% greater in the affecteds, 5.25 standard deviations above reference normals. Among the adult male members of the kindred, spine BMC and BMD were about 63% and 37% greater, respectively, in the affected individuals and over 4 standard deviations greater than reference normals. Findings in the hip were similar.

There are a number of known phenotypes exhibiting high bone mass that have distinguishing characteristics[4] and distinct clinical syndromes of disease. Most come to medical attention because of clinical symptoms, usually rather severe, or specific diagnostic radiographic features, or both, and some of them have now been shown to result from Lrp5 mutations[5]. Some exhibit localized skeletal lesions rather than a generalized skeletal condition as we see here. Some of the recent reports of the phenotypes occurring with gain of function mutations in Lrp5 have described oro-maxillo-facial ("torus") abnormalities[5,6], and some have not[2]. Our kindred provides an interesting insight on this aspect of the phenotype. We believe the mutation causing the phenotype in this kindred is of interest in understanding skeletal physiology. It determines peak bone mass since it is expressed in childhood and young adulthood. Further, its influence persists throughout life into the ninth decade. The cortex of long bones is slightly thicker, and trabeculae are thicker as well. The medullary cavities and hematopoietic marrow space are smaller, but there is no interference with hematopoiesis. The phenotype does not match other disorders of bone such as progressive diaphyseal dysplasia (which we mistakenly misdiagnosed at the beginning of the study), pycnodysostosis, or melorheostosis. Two general hypotheses of mechanisms causing the high bone mass phenotype in our kindred can be suggested: 1. The mutation causes a general increase in all pathways stimulating proliferation and work of osteoblasts, or 2. The mutation functions through mechanism(s) in the skeleton that sense mechanical loading, and the mutation causes increased sensitivity resulting in over-adaptation to normal mechanical loads. We favor the second explanation.

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