

## INVITED EDITORIAL

# Searching for Gene Defects That Cause High Bone Mass

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Bone is not cement. Not only to serve a structural role but to act importantly in biochemical processes, osseous tissue is alive and complex and consists of a mineral phase and a matrix phase that together are constantly being degraded and then reformed throughout the skeleton. This process of bone breakdown and bone formation, called *remodeling*, is mediated by specific cell types (osteoclasts and osteoblasts, respectively) that function in health in a highly coordinated fashion. Development of the adult skeleton is more complicated, involving *growth* and *modeling* (shaping) of individual bones while remodeling is lifelong (Marks and Hermey 1996).

### Dense Bones

In some individuals, the growth, modeling, and/or remodeling of the skeleton are disturbed in such a way that skeletal mass is increased. Dense bones may occur because there is excessive formation and/or defective degradation of osseous tissue. The term *osteosclerosis* refers to increased density of trabecular (spongy) bone, whereas *hyperostosis* refers to thickening of cortical (compact) bone from deposition of osseous tissue along subperiosteal and/or endosteal surfaces. High bone mass can result from osteosclerosis and/or hyperostosis occurring focally or throughout the skeleton (Frame et al. 1987).

Typically, metabolic, neoplastic, hematologic, or nutritional disturbances are the etiology of dense bones. Occasionally, however, heritable conditions are the explanation. Although individually rare, there are  $\geq 20$  well-recognized genetic causes of increased skeletal mass (Frame et al. 1987; Whyte 1996). Furthermore, new genetic disorders featuring dense bones continue to appear in the literature, and this list of conditions will continue to grow.

Understandably, the nosology for heritable forms of dense bones has been essentially a clinical/radiological/genetic construct (Frame et al. 1987; Whyte 1996). For only a few of these disorders is the pathogenesis established; the best understood are the osteopetroses, in which histopathological studies incriminate a failure of osteoclast-mediated resorption of skeletal tissue (Whyte 1992). Primary spongiosa, the calcified cartilage that is deposited during endochondral bone formation at growth plates, is not remodeled away by osteoclasts and can be seen encased within trabecular bone on microscopic examination (Whyte 1992). Pycnodysostosis, the disorder that some speculate affected the French impressionist painter Henri de Toulouse-Lautrec (1864–1901), results from cathepsin K deficiency (Gelb et al. 1996). A patient with craniometaphyseal dysplasia has been reported to have low levels of a hydrogen-ion pump in osteoclasts (Yamamoto et al. 1993). The pathogenesis of other heritable disorders that cause dense bone is more nebulous.

### Molecular Investigation of Dense-Bone Diseases

Molecular studies have revealed the etiology of just two diseases that cause dense bones in humans. Among the at least eight true forms of osteopetrosis in man (Whyte 1992), only the autosomal recessive syndrome known as *osteopetrosis/renal tubular acidosis/cerebral calcification* is delineated at the gene level. In this inborn error of metabolism, a variety of defects in the carbonic anhydrase II isoenzyme gene have been identified (Sly and Hu 1995). In fact, the chromosomal locations of other types of osteopetrosis (some autosomal dominant, some autosomal recessive) remain unknown (Whyte 1992). Recently, pycnodysostosis became the second of the dense-bone diseases to be understood at the molecular level, when mutations were discovered in the cathepsin K gene (Gelb 1996).

In this issue of the *Journal*, Johnson et al. (1997) describe a kindred in which high bone mass has been inherited as an autosomal dominant trait. Because high bone mass affects young adults as well as elderly family members, it is apparent that peak bone mass is increased. Nevertheless, affected individuals appear to be asymptomatic. Reportedly, cortical bone is thickened on

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endosteal surfaces (I anticipate that the radiological and perhaps histopathological studies of bone will be depicted in detail elsewhere). Perhaps this reflects a failure of endosteal bone resorption, rather than hyperostosis (Frame et al. 1987; Resnick and Niwayama 1995). Assays of biochemical markers that reflect skeletal turnover, however, suggest that this disorder is associated with a normal rate of bone remodeling. I wonder whether this kindred has the so-called Worth type of endosteal hyperostosis (Adès et al. 1994). Importantly, Johnson et al. report mapping studies that provide strong evidence that the gene responsible for the high bone mass in this kindred is located on chromosome 11q12-13, which is of interest because this is the region where the phenotype known as *osteoporosis pseudoglioma syndrome* recently has been localized (Gong et al. 1996).

### Why Study Dense Bones?

Although genetic disorders that cause dense bones are rare and some are mere radiological curiosities (Frame et al. 1987; Resnick and Niwayama 1995; Whyte 1996), searching for their molecular explanations is a worthwhile quest. Osteoporosis, the converse clinical problem, is a major health concern in the United States and elsewhere (Ray et al. 1997). In this condition, the mineral:matrix ratio of bone tissue is essentially normal, but there is insufficient trabecular and/or cortical bone mass to meet the body's structural requirements. In fact, osteoporosis is estimated to affect 10 million individuals in the United States. Most are women who have the most prevalent type—postmenopausal osteoporosis. In the United States, osteoporosis is a factor in an estimated 300,000 hip fractures/year and is a significant cause of morbidity and mortality, especially for the elderly. The cost associated with osteoporotic fractures recently has been estimated as having been \$13.8 billion in 1995 in the United States (Ray et al. 1997).

Estrogen-replacement therapy can help to preserve skeletal mass in women at menopause and thereby can help to decrease their risk of osteoporotic fractures. In addition, the bisphosphonate alendronate and synthetic salmon calcitonin are FDA-approved drugs for postmenopausal osteoporosis and also act principally by blocking bone resorption. Sodium fluoride continues to be investigated (Marcus et al. 1996). However, newer drugs that can safely and substantially increase skeletal mass with good quality bone are needed. With the advancing age of the baby boomer population in the United States, the problem of osteoporosis and fracture will continue to grow (Ray et al. 1997). Hence, improved understanding of the factors that condition peak skeletal mass or that regulate bone remodeling are crucial. Heritable disorders that cause high bone mass are

“experiments of nature” that should disclose additional approaches to low-bone-mass problems.

### Genetic Determinants of Bone Mass

As Johnson et al. discuss in their report, family and twin studies support an important genetic effect on peak bone mass (Sambrook et al. 1996). Studies using biochemical markers of skeletal turnover suggest that the genetic influence on bone-mineral density is mediated through regulation of bone remodeling. It is unclear, however, whether a genetic effect exists on rates of bone loss with aging or after menopause. Studies of the heritability of bone density suggest that ~60%–80% of the adult peak skeletal mass is genetically predetermined (Sambrook et al. 1996). Some investigators report that the gene that encodes the vitamin D receptor (VDR) may be a critical factor (Fleet et al. 1995). Certain polymorphisms in the VDR gene have been associated with low bone-mineral density, in studies of some but not all populations (Fleet et al. 1995; Looney et al. 1995). This is a controversial topic in the field of osteoporosis research (Van Leeuwen et al. 1996). Understandably, attention is now also being directed to identify other genes that might be associated with familial osteoporoses.

### Mapping Bone-Density Genes

Currently, efforts are underway to identify suitable kindreds or families in whom genomewide searches may disclose genes that are important in conditioning skeletal mass (Spotila et al. 1991, 1996). Elucidation of the molecular basis of osteogenesis imperfecta, a considerable variety of mutations in the genes that encode the pro  $\alpha 1(I)$  and pro  $\alpha 2(I)$  chains that constitute the type I collagen heterotrimer, has revealed the etiology of this relatively rare form of familial osteoporosis (Byers 1995). However, bone is a complex tissue, and mutations in any of the bone-specific structural proteins involved in mineralization and remodeling might be involved in additional forms of osteoporosis. Other regulatory pathways, reflected by the strong genetic influence on biochemical parameters of bone formations and breakdown, could be defective (Sambrook et al. 1996).

### Conclusion

Families with heritable disorders that cause dense bones are one of nature's windows on genetic factors that condition skeletal mass. The report by Johnson et al. is welcome progress from this resource. Molecular studies should be matched by equally intensive investigation of the clinical, radiographic, histopathological, and biochemical nature of these conditions, so that the mech-

anism by which the gene defect causes high bone mass will be understood.

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