0021-972X/97/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 82, No. 4
Printed in U.S.A.

Editorial: The Search for the Osteoporosis Gene*

The new definition of osteoporosis as a disease of low bone mass and increased fracture risk (1) is an important paradigm shift that may affect many of our previous notions of this disease. It has become essential to document the expected peak adult bone mass for populations and the factors that affect the accumulation and loss of peak adult bone mass. Before 1991 osteoporosis was recognized only by the occurrence of fragility fractures, which are now regarded as complications of the disease rather than manifestations of the disease itself.

While it has long been accepted that there is a large heritable component to bone mass, until recently this has been based on twin studies and epidemiologic surveys of family history of osteoporosis rather than genetic data *per se*. The use of fracture data in estimating the prevalence of osteoporosis in a family or population has been questionable because it is difficult to determine whether a fracture resulted from trauma or from low bone mass (osteoporosis). For example, many patients (and their physicians) fail to recognize that there are many causes for loss of height, vertebral deformities, and increased thoracic kyphosis besides osteoporosis. The common distal forearm (Colles') fracture following a simple slip and fall is still more often regarded as a "traumatic" rather than an osteoporotic fracture. Very few women who sustain a Colles' fracture in the few years after the menopause are referred for evaluation and management of osteoporosis.

Despite these shortcomings, it is still reasonable to conclude from a substantial body of literature that there is a strong hereditary or genetic component to osteoporosis and its complication of fragility fracture. It not surprising that a great deal of effort has recently been placed on finding the "gene(s)" for osteoporosis. Nor is it surprising, given the range of variation in estimates of the prevalence of osteoporosis and the multifactorial pathogenesis of fragility fractures, that this search has led to a plethora of confusing and conflicting results. This situation is all too familiar from studies on the genetics of other very prevalent endocrinopathies such as diabetes (2) and hypertension (3). Recent reviews on the genetics of osteoporosis have, for the most part, simply catalogued the data without resolution.

In this issue of JCEM (see page 991), Han and colleagues (4) report a negative study of the contribution of polymorphism within the estrogen receptor gene (ERG) to bone density and the response to hormone replacement therapy in 248 Korean women. The ERG is a reasonable candidate gene, given the cause and effect relationship between estrogen deficiency and bone loss and a very incomplete understanding of the significance of polymorphism in this gene. The pioneering work of Morrison, *et al*. in Australia (5) with the vitamin D receptor gene (VDRG) was also a reasonable approach to finding a candidate gene for osteoporosis because of the integral relationship between vitamin D and skeletal metabolism. The complex biology of the skeleton, with so many factors involved in skeletal growth and development, and the universal nature of age-related bone loss make it extremely unlikely that there is a single gene for osteoporosis. However, this would only explain why the genetic markers studied to date account for only a small part of the variance in bone mineral density (BMD) and would not explain the conflicting data concerning individual genes.

There are at least two places to look for explanations for the apparent discrepancies in genetic studies of bone mass and osteoporosis. First, so many factors affect adult bone mass that a single time-point measurement in a postmenopausal woman will reflect an extremely variable, genetically determined component and an extremely variable component that has resulted from individual life events. The latter would include diseases, drug exposures, reproductive and menopause history, and possibly dietary and physical activity variables. Even peak adult bone mass in young adults is assumed to be affected by such factors, a concept that has stimulated much research on strategies for maximizing peak adult bone mass. After some point in early middle age, bone loss ensues and is a universal phenomenon related to aging (6). The rate of bone loss varies among individuals and is another factor in measured bone mass, in an adult, that may or may not be under strong genetic control.

The second reason for variable results in genetic studies of bone mass is that the nature and frequencies of genetic polymorphisms vary among populations. Some allelic variants of a gene are virtually absent in some populations (such as the Type B blood group in aboriginal Native American populations) (7). In some groups one or more allelic variants have a relatively high prevalence, while appearing only with very low frequency in other populations. A classic example of this situation is the hemoglobin variants such as Hb^S that are found in malarial areas in sub-Saharan Africa, Saudi Arabia, India, and parts of the Mediterranean (8). The explanation for polymorphic variation in genes and for the varying clinal distributions of genotype frequencies across populations (9) is found in the post-Darwinian synthesis of evolutionary theory. This holds that mutations—changes in genetic material—are the source of new hereditary material (10). They occur randomly and at varying rates at most if not all genetic loci. The new alleles that result are either lethal or deleterious, in which case they remain rare in a population, or they are neutral or advantageous. In the latter two cases, the other forces of evolution act upon the frequency of the new alleles, increasing or decreasing them depending on the population's specific circumstances. Genetic drift can increase an allele's frequency by random fluctuations in a small popu-

Received February 13, 1997. Accepted February 14, 1997.
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* Supported in part by a grant from the Barbara Ann Karmanos Cancer Institute, Detroit, Michigan.

lation, and gene flow can move alleles among populations, thus increasing or decreasing the prevalence. Natural selection, first described by Charles Darwin, is the primary force that favors bearers of advantageous genetic combinations through increased reproductive success or, conversely, weeds out disadvantageous ones through decreased fertility. In this frame of reference, it should not be surprising that ERG and VDRG polymorphisms are found in different frequencies in different populations. Thus, study results from as disparate populations as Australian Whites (4), Japanese (11), Korean (4), English (12), US Blacks and Whites (13), etc., are expected to be different. The more difficult question is why the associations between allelic variants in these genes are sometimes found and sometimes not, and sometimes found in opposite directions. It is important to remember the first reason for these conflicting findings—that measured bone mass in an adult is the result of a myriad of environmental influences acting on the genetic potential for peak bone mass and, presumably, rate of bone loss. Studies must be done in extremely large samples that can control for multiple confounders, or they must be done at the maximum point of bone accumulation in young adults, again in large samples. A recent meta-analysis of the VDRG by Cooper, *et al*. (14) has demonstrated that disparate individual studies, when merged, do begin to make some sense of the variation. Working with data from 29 study groups, they found that there were indeed differences in BMD at the hip and the spine. Importantly, they found a trend ($P = 0.06$) towards the difference in hip BMD between the genotypes being larger in younger women and decreasing with age. This is in keeping with our first postulated explanation for lack of concordance between studies.

We would expect that, based on the analogy between the Vitamin D receptor's relationship to bone and the estrogen receptor's relationship to bone (15), the pooling of data from many studies like Han *et al*. (4) will eventually settle whether the ERG polymorphisms contribute to the genetics of bone mass. Until then, we must be open-minded and receptive to findings from as many centers as possible, in as many populations as possible. The ultimate questions for both receptor genes are why they are variant, why the prevalence of genotypes varies among populations, and what this means for the evolutionary history of the disease osteoporosis. Only when these are answered will we have clues to the future and, hopefully, ways to counter the alarming rise in the prevalence of osteoporosis (16).

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