Genetics of Osteoporosis

Laura Masi, Luigi Gennari, Alberto Falchetti, and Maria Luisa Brandi

Introduction

Understanding the genetic base of multifactorial diseases represents the future task for scientists in order to explain new physiopathological aspects of complex traits. One of these diseases is represented by osteoporosis (OP).

OP is a common disorder associated with reduced bone mineral density, affecting up to 40% of women and 12% of men at same point during life. Osteoporotic fractures are an increasing health care burden in all aging communities. A major determinant of fracture risk is represented by bone mineral density (BMD), independent of other factors such as aging per se and falls [1]. BMD depends upon both the peak bone mass achieved in adolescence and the subsequent bone loss. However, peak bone mass is the major determinant of bone mineral density for up to 10-20 years after menopause, until age-related factors become relatively more important in determining bone mass loss. Although OP is a multifactorial trait, genetic factors play an important effects on peak bone mass and in the pathogenesis of OP. The development in advanced techniques for measuring BMD made possible to have available a quantitative trait for segregation analysis. In fact, quantitative traits are defined as characters that everyone has, that are measurable and that exhibit a normal distribution in the population. Up to 75% of variation in BMD has been suggested to be under genetic influences [2]. However, the inclusion of OP in the list of genetic disorders is still debatable. Twin studies have shown a strong genetic effect of BMD at both peripheral and axial sites [2]. The largest genetic influence was observed at sites of high trabecular bone content. Although twin studies have been powerful tools for studying genetic effects, they show some limitations and can only imply but not prove genetic influence. A variety of experimental design appropriate models for establishing genetic background of OP have been proposed, such as linkage analysis, allele sharing methods, association studies, and experimental crosses [3] (Figure 1).

Family studies suggest a significant effect of genetic factors on peak bone mass. For example, using the early approach of metacarpal/cortical bone thickness, parent-offspring correlations indicated that bone mass was for a large portion genetically determined [4]. In addition sib-pair studies, in premenopausal daughters of women with OP, have also shown modest but significant reductions in lumbar spine, femoral neck, and femoral shaft BMD compared to premenopausal women without a family history of OP [5].

R. Pauletta et al. (eds.), Women’s Health and Menopause. 117–123.
In the last five years association studies have provided new and controversial information. The studies have compared allele frequencies for a particular polymorphism or candidate gene in disease population with that in nondisease population. Despite linkage analysis, where a physical connection between trait and marker locus must exist, an allele can be considered associated with a trait when it occurs more frequently in individuals with the trait than those without the trait. It confers an increased risk for disease to individuals carrying the associated allele (Figure 2). These studies have used the candidate gene approach and, given the number of factors that are likely to be involved, there is a seemingly unlimited supply of candidate genes for OP.

Discrepancy among studies can be explained on the basis of the quantitative polygenic nature of this disorder, where the effect of a given gene can easily be modified.