Genetic aspects of osteoporosis

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Bone characteristics in both animal models and humans are quite heritable; approximately 60-80% of the variability in bone mineral density is explained by genetic influences [1]. Other important skeletal characteristics are also heavily influenced by genetics, including bone length, size, and material properties. Despite the importance of genetics in determining these traits, the identification of the specific genes involved, and the mechanisms by which they operate, has been challenging.

In a number of congenital disorders, such as osteogenesis imperfecta and hypophosphatasia, the responsible genes are well known (type 1 collagen and alkaline phosphatase, respectively). Conditions like these are inherited in a Mendelian manner and classical genetic methods, supplemented by modern molecular techniques, can be very effective in identifying new genes of interest. As an example, in some families bone mass is inherited in an autosomal dominant manner and study of some of these kindreds has identified \textit{Lrp5} as a novel effector of bone mass [2]. In fact, the identification of \textit{Lrp5} as an important gene in these families also revealed that it was involved in a previously unrecognized biochemical pathway very important in bone — that involving \(\beta\)-catenin signaling.

On the other hand, it has been more difficult to uncover the genes responsible for the variation in bone strength in the general population. A variety of candidate genes have been proposed, including type 1 collagen (\textit{Col1}), estrogen receptor, vitamin D receptor, IL-6, etc. [3]. A major challenge in population studies is that there are apparently many genes involved in the regulation of bone character, each of which contributes a small fraction of overall variability. For instance, polymorphisms in the \textit{Lrp5} and \textit{Col1} genes appear to contribute to variation in the general population, but each to a very limited extent (<5% of the variation in BMD) [4]. Under these circumstances, adequate experimental power for the identification of contributing genes often demands studies that involve many thousands of individuals. Whereas there are many reports of gene effects noted in smaller study populations, there is great concern that the conclusions from these analyses may be suspect because of the limited study power.

Studies in inbred mice models have been very useful in identifying novel genes of importance in bone, and yield great opportunities to discover new genes and molecular pathways. For instance, several related genes related to osteoblast stem cell differentiation, including \textit{Alox15}, have been identified as having influences on bone mass [5]. These and related genes apparently affect the rate at which stem cells differentiate into osteoblasts (with a positive effect on bone mass) or adipocytes (with a negative effect on bone mass).

Despite the promise of this kind of translational research, the impact of these and other candidate genes discovered in animal models has not been fully examined in human populations. In part this is because there are many challenges to testing genes discovered in animals in human populations. For instance, even if a compelling gene is discovered in mice the number of polymorphisms in human genes is very large and understanding if and how these polymorphisms may affect bone, alone or in combination with other polymorphisms (including those in other genes), is very complex. Moreover, genetic differences based on race and geography make it important to test gene — phenotype relationships in several separate populations. Nevertheless, with continued effort, knowledge of genetic mechanisms promises to provide major advances in pathophysiology, diagnosis and therapy of osteoporosis. For example, testing for genes that impart risk may aid in the selection of patients for therapy. Or, the understanding of genetic mechanisms may reveal opportunities for new therapeutic interventions.

REFERENCES