Regulation of skeletal development - Insights derived from genetic disorders

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Development of the vertebrate skeleton is a complex process involving regulation at many levels. At early stages patterning genes and differentiation factors control the spatial condensation and differentiation of mesenchymal cells to osteoblasts (in membranous bones) or chondrocytes (in cartilage anlagen). Local signalling events regulate cell proliferation and apoptosis and control the shape and size of skeletal elements. Finally, extracellular matrix production and degradation contribute to skeletal remodelling and homeostasis.

In our laboratory we have taken a genetic approach to gain insights into the genes that regulate these processes. In families with distinct inherited disorders of skeletal development we have used linkage mapping to determine the chromosomal loci of the responsible genes, followed by positional candidate gene cloning and analysis to find the disease-causing mutations.

The identified gene mutations provide detailed information about skeletal patterning and growth, cell differentiation, and cellular interactions. For example, in pedigrees with synpolydactyly, polyalanine expansions within HOXD13 provide direct evidence for patterning and growth control functions of HOXD13 during limb development. In individuals with cleidocranial dysplasia, characterized by deficient ossification of sutures and fontanelles in the skull, partial or complete absence of the clavicle and tooth abnormalities, heterozygous loss of function mutations in the transcription factor CBFA1 demonstrate that this factor has an essential role in osteoblast differentiation. Finally, in families with craniometaphyseal dysplasia, characterized by excessive bone formation in the craniofacial skeleton, or in families with cherubism, characterized by age-related excessive bone remodelling and loss in the maxilla and the mandible, identification of the responsible genes promises to reveal novel aspects of the balance between osteoblasts and osteoclasts.