

## THE MOLECULAR AND CELLULAR CHANGES UNDERLYING INCREASED BONE FORMATION IN A MOUSE MODEL WITH GENERALIZED PROGRESSIVE HYPEROSTOSIS

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**INTRODUCTION:** Schmid metaphyseal chondrodysplasia (SMCD) is an autosomal dominant disorder caused by mutations in *COL10A1* gene, characterized by drawfism, *coxa vara* and flaring of the metaphysis. The majority of the mutations reported are clustered within the carboxy-terminal NC1 domain. These mutations are thought to impair trimer assembly that initiates from the NC1 domain. To study the pathological and molecular consequences underlying this disease, we have produced transgenic mice expressing a SMCD mutation in the mouse collagen X gene, a 13-bp frame-shift deletion in the NC1 domain. The phenotypes of the mice showed characteristics of SMCD such as drawfism, shortened limbs (figure 1) and growth plate abnormalities.



Fig. 1: collagen X gene mutant mouse (right) show characteristics of SMCD patients such as drawfism and short limbs when compare with a wildtype mouse (left).

However, we observed an additional phenotype of generalized progressive hyperostosis, which is not seen in SMCD patients, with thickening of bones (figure 2), suggesting deregulated bone growth and/or remodeling. Bone remodeling is important in maintaining the quality and quantity of bone and mineral homeostasis. It involves two tightly-coupled but opposing events, bone formation and bone resorption which are carried out by osteoblasts and osteoclasts, respectively. Normally, bone formation is in balance with bone resorption to maintain a constant bone mass.

Altered balance between these two processes can lead to hyperostosis (too much bone) or osteoporosis (not enough bone).

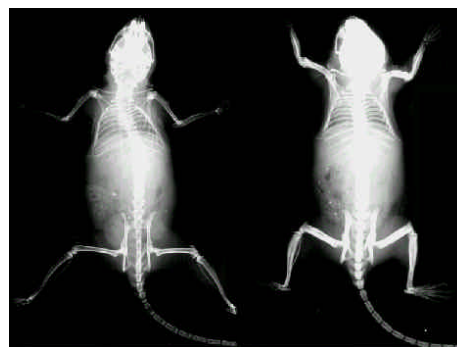


Fig. 2: X-ray shows the bone density of the entire skeleton in transgenic mouse (right) is higher than non-transgenic littermate (left).

**METHODS:** Using *in vivo* and *in vitro* approaches, we systematically analyze parameters for osteoblast and osteoclast activities in this transgenic mouse model.

**RESULTS:** Osteoclast analysis indicated that the number and activity are not reduced, suggesting that altered resorption is not a major contributing factor. However, *in situ* hybridization showed that osteoblasts are more active in producing Collagen I, a major bone matrix component. Cultured osteoblasts supplemented with serum derived from transgenic mice showed elevated Collagen I synthesis compared to that of non-transgenic serum, strongly suggesting that a humoral factor is stimulating osteoblast function in this transgenic mouse.

**DISCUSSION & CONCLUSIONS:** Work is currently underway to identify this systemic factor. Uncovering the molecular basis for bone overgrowth in these mice will provide insight into the regulation of bone formation and the potential for discovering new drugs that can stimulate bone formation. This will be clinically relevant for the treatment of osteoporosis and allied conditions.

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