

# OSTEOSCOOP

News on current events in osteoporosis and rheumatology

## A new gene involved in osteopetrosis

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Osteopetrosis is a genetically and clinically heterogeneous bone disorder characterized by a reduction in bone resorption and a generalized net accumulation of skeletal mass. The causative genes identified so far all play a role in acidification of the resorption lacuna, and loss-of-function mutations in these genes severely affect mature osteoclast function. The *CA2* (carbonic anhydrase 2) gene produces the protons necessary for acidification of the resorption lacuna, the extracellular compartment between the bone tissue and the osteoclast where bone resorption occurs. The  $\alpha 3$  subunit of the  $H^+$  ATPase is involved in the transportation of these protons through the ruffled border into the resorption lacuna, while chloride channel 7 (ClC-7) translocates chloride ions to maintain electroneutrality.

In animals, osteopetrotic mutations affecting both formation and function of osteoclasts have been described. One of the spontaneous mutations is the *incisors absent* (*ia*) rat which exhibits a generalized skeletal sclerosis and delay of tooth eruption. These mutants have 2 to 3 times more osteoclasts than do normal littermates, and *ia* osteoclasts lack ruffled borders but contain numerous small cytoplasmic vesicles containing tartrate-resistant acid phosphatase, suggesting a dysfunction of the secretory pathways.

In this study [1], the gene responsible for *ia* mutation has been identified as *pleckstrin homology domain-containing family M (with RUN domain) member 1* (*PLEKHM1*). Loss-of-function mutations of this protein underlie the osteopetrotic phenotype of the *ia* rat as well as an intermediate type of human osteopetrosis. Monocytes from a patient homozygous for the mutation differentiated into osteoclasts normally, but cultured osteoclasts failed to form ruffled borders and showed little evidence of bone resorption.

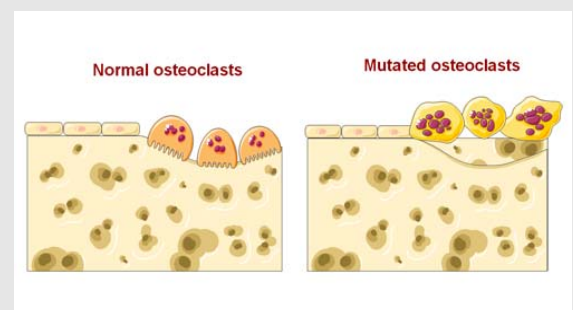
In conclusion, *PLEKHM1* appears to be a novel gene implicated in the development of osteopetrosis, with a putative critical function in vesicular transport in the osteoclast.

1. Van Wesenbeeck L et al. *J Clin Invest.* 2007;117:919-930.

### A new gene involved in osteopetrosis

Mature osteoclasts are multinucleated cells with a well-developed ruffled border, anchoring zones to bone, and the ability to acidify the resorbing lacuna because they secrete protons.

Mutated osteoclasts are as numerous as normal ones and are multinucleated. However, they do not exhibit ruffled borders and their resorptive capacity is severely impaired. This pattern may result from an abnormal secretory pathway of membrane proteins involved in bone resorption.



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