

Juvenile Paget's disease: a "flip side" of hypophosphatasia

Whereas hypophosphatasia is characterized by abnormally low levels of alkaline phosphatase, children with hyperphosphatasia, or juvenile Paget's disease (JPD), have too much of the enzyme in their bodies.

Only about 40 children worldwide have been diagnosed with JPD, a painful skeletal disease characterized by abnormally fast formation and breakdown of bone throughout the body.

By separately tackling genetic, patient-oriented studies and cellular research, two School of Medicine research teams have discovered—almost simultaneously—two distinct causes of JPD.

In the clinically motivated study, published in the July 18, 2002 issue of the *New England Journal of Medicine*, Michael P. Whyte, MD, Steven Mumm, PhD, and colleagues identified the first genetic cause of JPD.

The researchers found that two seemingly unrelated Navajo Americans with juvenile Paget's disease were completely missing the gene for a recently discovered protein called osteoprotegerin, known to protect bone.

Using information from the Human Genome Project, the team also was able to pinpoint exactly where DNA had broken off in both patients. The results were identical for the two patients studied.

In a separate animal study led by F. Patrick Ross, PhD, research professor of pathology and immunology, researchers discovered a mouse model of JPD. Those results appear in the September 2002 issue of *Nature Medicine*.

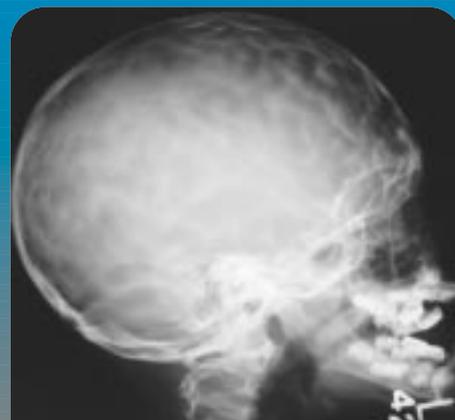
Mice engineered to lack the gene for SHIP (Src homology 2-containing inositol-5-phosphatase) have abnormally high numbers of macrophages, a type of immune cell. Because macrophages can develop into osteoclasts (cells that break

Two heritable bone disorders, extremely different levels of one enzyme



HYPERPHOSPHATASIA

Alkaline phosphatase: Too much? Too little? The skull of a teenager with juvenile Paget's disease has markedly thickened, left. Painful headaches can result; cranial nerves are endangered.



HYPOPHOSPHATASIA

The plates in the child's skull at right fused prematurely. The no longer expanding skull has the dimpled appearance of hammered copper—considered to be the impressions of the still-growing brain inside. Cranial surgery enables expansion.

down bone), the team hypothesized that mice lacking SHIP may eventually develop symptoms similar to JPD.

They were right. The mice had twice as many osteoclasts as normal mice, and the cells were much larger than normal. When the team examined cell samples in petri dishes, macrophages from mice lacking SHIP not only rapidly developed more osteoclasts than normal, the osteoclasts also lived longer. Moreover, they broke down bone much faster than normal osteoclasts. In other words, these cells looked suspiciously similar to osteoclasts in people with JPD.

With too many enlarged osteoclasts, the mice had shorter, less thick bones, lost about 22 percent of their bone-mineral density, and were far more susceptible to bone fractures: again, all hallmarks of juvenile Paget's disease in humans.

In summary, absence of either osteoprotegerin or SHIP leads to enhancement of the same signaling pathway, which is central to the formation and function of osteoclasts. These findings suggest that a common mechanism may mediate several forms of a devastating bone disease.

The two groups believe their complementary findings provide valuable insights into the process of bone formation and breakdown, and that these lines of research may ultimately lead to new treatments for a variety of metabolic bone diseases.

Steven L. Teitelbaum, MD, the Wilma and Roswell Messing Professor of pathology and immunology, says: "These two studies highlight the successful marriage between clinical and basic science in bone research groups at Washington University School of Medicine."