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Researchers Discover "Thermostat" that Regulates Bone Density

Researchers tracking the cause of a rare genetic disorder that causes brittle bones have discovered a genetic "thermostat" that appears to control the accumulation of bone mass during growth. The findings could substantially increase understanding of why many people fail to achieve sufficient bone mass during the first three decades of life, a significant risk factor for the development of osteoporosis.

Osteoporosis is the underlying cause of more than 1.7 million hip fractures annually worldwide. In the United States alone the cost of treating osteoporotic fractures approaches \$15 billion annually.

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— Matthew L. Warman

In an article published in the November 16, 2001, issue of the journal *Cell*, an international consortium of 62 clinicians and scientists led by Howard Hughes Medical Institute investigator Matthew L. Warman reported the discovery of the cause of the inherited disorder, osteoporosis-pseudoglioma syndrome (OPPG). Studies of families with OPPG led the researchers to mutations in a completely unsuspected gene called *LDL receptor-related protein 5 (LRP5)*, which codes for a protein whose precise cellular function remains unknown.

"I became interested in this extremely rare disease in 1993 after meeting three affected patients," said Warman, who is at Case Western Reserve University and University Hospitals of Cleveland. "Their severe symptoms of very brittle bones and progressive blindness convinced us that this was an important disease to solve. So, with the support of my mentor, professor Bjorn Olsen at Harvard Medical School, we formed an osteoporosis-pseudoglioma collaborative group to enlist affected families and their physicians in this effort."

Although the researchers were able to identify the region of the genome that apparently harbored the gene mutation responsible for OPPG, they did not zero in on the gene responsible until a good working draft of the human genome sequence became available. This led the research team to *LRP5*.

According to Warman, genetic studies in several families revealed different types of mutations that eliminated function of the protein produced by *LRP5*. The scientists then showed in mice that the *Lrp5* gene was expressed in bone-forming cells, called osteoblasts, and that the gene's activity appeared to increase during differentiation of cells into osteoblasts during bone formation.

Despite these discoveries, one key piece of information was still missing. "We needed to know which signaling pathway was affected by the loss of the LRP5 protein," said Warman. One clue arose from the fact that a relative of LRP5, called LRP6, had been shown to function in a signaling pathway involving a protein called Wnt.

"It was known that the Wnt family of growth factors is involved in many different developmental processes, such as brain and limb patterning," said Warman. "But I don't think anyone had directly implicated Wnts in determining the quantity of bone that is formed."

In addition to implicating LRP5 in bone density, "a second surprise was that carriers of single *LRP5* mutations—who have half the normal complement of functional *LRP5* genes—also showed reduced bone mass when compared to normal individuals. Thus, LRP5 appears to be something like a bone 'thermostat' that controls the level of bone mineralization," said Warman.

These findings suggest that enhancing the function of the *LRP5*-signaling pathway could increase bone density, not only in people suffering rare, severe bone disorders such as OPPG, but also for people with subtler deficiencies in bone mass.

"For the OPPG patients, these findings suggest that they do not necessarily make defective bone; they just make insufficient bone," said Warman. "So, if we can discover treatments that bypass this LRP5 signaling cascade, in order to get these patients to make more bone, we may cure their bone disease," he said.

"And for the general population, the findings of a dosage effect suggest that normal genetic variation with this gene might contribute to normal variation in bone strength within the population. Even more exciting, these results suggest that finding a way to pharmacologically manipulate or regulate this gene, or the pathway in which it acts, might allow us to 'dial up' everybody's bone mineral density. If we're able to do that, it might provide a very powerful tool for preventing osteoporosis," said Warman.

Warman and researchers in the consortium will now concentrate on exploring the effect of genetic variants of *LRP5* in other populations of patients with bone disorders. Also, he said, research groups including his own have

developed mice with altered *Lrp5* genes that will allow more detailed understanding of the signaling pathway involving *Lrp5* and *Wnt* . There is also evidence that a genetic trait in humans that causes higher-than-normal bone density maps to the same genomic region that contains *LRP5* , implying that other mutations in *LRP5* may enhance bone growth, said Warman.