Team identifies genes influencing bone density

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School of Medicine researcher Charles Farber and his team identify genes influencing bone density.

(Medical Xpress)—Geneticists have taken a major step forward in the battle against osteoporosis by identifying two genes that play critical roles in regulating bone mineral density. By targeting those genes with

therapeutics, doctors may one day be able to manipulate bone density to prevent or cure the bone fragility that endangers the health of millions around the world.

The research offers important insights into the development of osteoporosis, providing a new understanding of the causes of the potentially debilitating condition.

"Currently there are over 12 million individuals in the U.S. who are diagnosed with osteoporosis, and another 30 million who are at high risk of becoming osteoporotic," said University of Virginia School of Medicine researcher Charles Farber, noting the tremendous impact the disease can have on a person's health and quality of life: "Roughly half of women and a quarter of men over the age of 50 in the U.S. will experience a fracture, and of those one in four will die within the subsequent 12 months."

Using an innovative new genetic technique to unlock our genes' secrets, Farber and his team determined that genetic variation in the gene Bicc1 regulates bone mass. They then determined how it was likely doing so – by influencing a second gene, Pkd2 – and showed that these genes play vital roles not just in lab mice, but in humans as well.

"There was a positive association between the levels of Bicc1 and the levels of bone mineral density, so the idea would be that if we can enhance the levels of Bicc1 in bone, that would be a very good thing for the skeleton," Farber said.

That finding could prove critically important for people with osteoporosis and those with a family history of osteoporosis, as the discovery opens up potential paths to preventing and treating the highly heritable condition.

"There are two facets to osteoporosis: the amount of bone you accrue early in life and the amount you lose with age. If you don't accrue enough or you lose bone more rapidly than most, then you at a higher risk for fracture," Farber said. "If we could promote Bicc1 activity at one or both stages, that may increase bone to the point of lowering fracture risk."

The research is also noteworthy for the novel method the scientists used to determine gene function. They figured out what Bicc1 does, in essence, by determining which other genes it works in tandem with. "We knew Bicc1 influenced bone mass, but we had no idea how it did this, so we simply asked what other genes its expression was correlated with," said Farber, of the U.Va. Center for Public Health Genomics. "What we found was Bicc1 was highly co-expressed with genes that play a role in bone-forming osteoblasts. This allowed us to predict that Bicc1 was also involved in the function of osteoblasts."

Further, the researchers used this principle to specially pinpoint that Bicc1 interacted with Pkd2.

The success of the technique offers scientists an important new way to deduce gene function. "We took an approach that people thought would work and we've demonstrated that it can," Farber said. "It's a proof of principle that you can use this notion of correlation to pick out a very detailed interaction between two genes."

The findings have been published online in the *Journal of Clinical Investigation* and will appear in a forthcoming print edition.

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