Scientists identify a candidate gene for osteoporosis

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Today, researchers report the identification of a gene that may play a role in susceptibility to osteoporosis—the crippling disease that leads to bone fractures, especially of the hip and spine. The study, conducted by scientists at the Musculoskeletal Diseases Center of the Jerry L Pettis Memorial Veteran's Affairs Medical Center at Loma Linda, shows convincing evidence that a gene called *DARC* negatively regulates bone density in mice. The report appears online in *Genome Research*.

"If our finding using the mouse model is confirmed in humans, then we may be able to develop therapies that are based on inhibiting the function of the *DARC* gene," explains Dr. Subburaman Mohan, Ph.D., a Senior Scientist at the Loma Linda VA Medical Center and a Professor of Medicine and Biochemistry at Loma Linda University. "We will also be able to develop genetic screens to identify individuals who are at risk for osteoporosis."

According to the National Osteoporosis Foundation, osteoporosis affects 55% of Americans over the age of 50. Low bone mineral density (BMD)—the primary indicator of osteoporosis—is influenced by both genetic and environmental factors (e.g., diet or medication). But the genetic element has been difficult to characterize because bone growth is controlled by many genes, including those for various hormones, growth factors, signaling molecules, and structural components of bone and cartilage.

Previous genetic studies had pointed to a region on mouse chromosome

1 as containing a gene responsible for BMD regulation. In the current project, Mohan and his colleagues honed in on this region of chromosome 1 using a variety of molecular techniques, and they located a gene called *DARC* (Duffy Antigen Receptor for Chemokines) that exhibited different levels of expression in mice with higher BMD. The analogous chromosomal region has also been shown to influence osteoporosis in humans.

The protein encoded by *DARC* binds to chemokines—or small signaling proteins—that are involved in osteoclast formation. Osteoclasts break down bone in a process called bone resorption, releasing important minerals such as calcium, phosphate, and magnesium into the bloodstream. This causes a reduction in BMD.

To confirm the involvement of *DARC* in regulating BMD, Mohan's team characterized the skeletal phenotype of mice with and without the *DARC* gene. The *DARC*-knockout mice exhibited increased BMD and lower bone resorption compared to mice with the *DARC* gene, supporting the predicted role of *DARC* in hastening bone resorption. They also showed that antibodies to the *DARC* protein, which effectively blocked the action of *DARC*, inhibited the formation of osteoclasts.

Although the researchers have identified a number of DNA alterations in the *DARC* gene, they did not pinpoint the specific alteration that was responsible for the BMD differences between the two strains of mice. However, Mohan and his colleagues predict that changes in the amino acid sequence or alterations in regulatory regions of the *DARC* gene may lead to key functional changes.

"There are interesting differences between African Americans and Caucasians that could be associated with this gene," explains Mohan. "African Americans exhibit significantly higher BMD compared to Caucasians. Also, African Americans generally do not have the Duffy

protein on red blood cells, while Caucasians do. The potential genetic association between *DARC* gene variation and these traits in humans certainly makes it worthy of further investigation."

Source: Cold Spring Harbor Laboratory