New genetic regions linked to bone-weakening disease and fractures

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Thirty-two previously unidentified genetic regions associated with osteoporosis and fracture have been identified by a large, worldwide consortium of researchers, including Stanford Prevention Research Center chief John Ioannidis, MD, DSc. Variations in the DNA sequences in these regions confer either risk or protection from the bone-weakening disease. Many, but not all, of the regions encode proteins involved in pathways known to involve bone health.

The research shows that osteoporosis results from the combined contributions of dozens, if not hundreds, of genes. It also suggests many new avenues for anti-osteoporosis drug development.

"We're learning that the genetic architecture of disease is very complex," said Ioannidis, who is one of seven senior authors of the study and the methodological leader of the consortium. The research will be published online April 15 in Nature Genetics.

The unprecedented prospective meta-analysis — which involved 17 genome-wide association studies, 180 researchers and more than 100,000 participants — also identified six regions strongly correlated with the risk of fractures of the femur or lower back. However, the predictive power of the study for individuals is relatively low: Those with multiple risk-increasing variants are only about three to four times more likely than those with the fewest variants to have lower bone mineral density and experience fractures.

"As a result," said Ioannidis, "the next step of incorporating this information into basic patient care is not clear. Each variant conveys a small quantum of risk or benefit. We can't predict exactly who will or won't get a fracture."

Although factors such as body weight, build and gender are currently much more predictive of osteoporosis than any of the genetic variants identified in the study, the research identified many pathways involved in bone health. The biological relevance of the findings was confirmed by the fact that some of the pathways are already targeted by current anti-osteoporosis drugs. Other, previously unsuspected pathways will help researchers understand more about the disease and how to develop drugs to fight it.

The research belies recent frustration with the ability of genome-wide association studies, or GWAS, to live up to their early hype. When first introduced in 2005, many researchers predicted that GWAS — a way of quickly scanning whole genomes for minute differences associated with disease occurrence — would quickly identify critical mutations for many conditions. This optimistic assessment proved to be largely unfounded for complex conditions such as osteoporosis, type-2 diabetes and obesity, which likely involve the combined effects of many genes and environmental components.

This study suggests that the number of participants in most GWAS may need to be vastly expanded to render useful data.

"The real power of our study lies in the ability to generate prospectively a huge combined data set and analyze it as a single study," said Ioannidis. "It's likely that our expectations have been too high in terms of what single studies can accomplish. Each one of the many teams identified at most only one or two markers; many found none."

Instead, increasingly larger studies will be needed to identify genes important in disease. "In reality, there may be 500 or more gene variants regulating osteoporosis," said Ioannidis. "To find all of them, we'll need to study millions of patients. Is this unrealistic? I don't think so. Sooner or later this will be feasible."

With a few exceptions, people have all the same genes in their DNA as everyone else; it's one of the things that makes us human. But the way those genes are spelled in each person's DNA can vary — much like how some words are spelled differently in the United States and Britain (think "center" and "centre"). Our genomes are riddled with such differences, which sometimes affect the gene's function. Studies like this one correlate certain genetic spellings, or variants, with specific outcomes, such as low bone mineral density and fractures. Any one person can have several or none of the variants identified by the study.

The current study grew gradually out of a decade of research conducted by Ioannidis and a few colleagues. At the time, a few teams across the world were attempting to correlate variations in individual genes with the development of osteoporosis. "We were doing small studies here and there on popular genes," said Ioannidis, "and then we thought we should collaborate with other researchers to do a meta-analysis. That marked the beginning of the first consortium."

However, despite the researchers' enthusiasm, they were hampered by the lack of whole-genome information and had instead to focus on specific genetic clusters they suspected might be involved in osteoporosis. That changed with the advent of the first GWAS. "The technology kept getting better, and we began to recruit more people," said Ioannidis.

For the current study, teams around the world combined data from 17 genome-wide association studies focused on bone mineral density on

nearly 33,000 participants in North America, Europe, east Asia and Australia. Combining the study results allowed the researchers to identify even weak associations that would have been missed in any one study.

Together, the teams identified 87 regions of the genome for further study. They then analyzed these regions in an additional 34 studies of bone mineral density with a total of nearly 51,000 participants. This validation step narrowed the field to 56 associated regions — 32 of which had not been previously associated.

Finally, the teams checked to see if there was an association between those variants that affect bone mineral density and the actual prevalence of fractures. To do so, they compared the sequences, or spelling, of those regions among 31,000 people who had experienced fractures of the spine or femur, with that of more than 100,000 people who had not had a fracture. They found six variants that were significantly associated with fracture risk.

People with the highest number of variants associated with decreased bone mineral density were about 1.56 times more likely than people with an average number of variants to have osteoporosis, and those with the most of those variants associated with fracture risk were about 1.60 times more likely to have experienced fractures. Compared with those who had the fewest associated variants, they were about four times more likely to have either osteoporosis or a fracture.

When the researchers looked more closely at the regions identified by their analyses, they found many genes that had been previously implicated in bone formation and bone health: members of the Wnt signaling pathway that is important in many types of development, several involved in a pathway important to the differentiation of mesenchymal cells that become bone, and others involved in

endochondrial ossification during the formation of the mammalian skeleton.

"We saw many of these regions and genes clustering within specific types of pathways, which suggests certain disease mechanisms," said Ioannidis. "It certainly wouldn't be unexpected to eventually identify many more genetic regions involved in the regulation of osteoporosis and fracture risk."

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