Mini Review

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Osteoporosis, fracture risk predicted with new genetic screen

A new genetic screen may predict a person's future risk of osteoporosis and bone fracture, according to a study by a researcher at the Stanford University School of Medicine.

Specifically, the study, one of the largest of its kind, identified 899 regions in the human genome associated with low bone-mineral density, 613 of which have never before been identified.

Keywords: osteoporosis ● genetic screen

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Introduction

People deemed to be at high risk - about 2 percent of those tested - were about 17 times more likely than others to develop osteoporosis and about twice as likely to experience a bone fracture in their lifetimes [1]. In comparison, about 0.2 percent of women tested will have a cancer-associated mutation in the BRCA2 gene, which increases their risk of breast cancer to about six times that of a woman without a BRCA2 mutation.

Literature Review

Early identification of people with an increased genetic risk for osteoporosis could be an important way to prevent or reduce the incidence of bone fracture, which according to the National Osteoporosis Foundation affects 2 million people each year and accounts for $19 billion in annual health care costs.

There are lots of ways to reduce the risk of a stress fracture, including vitamin D, calcium and weight-bearing exercise," said Stuart Kim, PhD, an emeritus professor of developmental biology. "But currently there is no protocol to predict in one's 20s or 30s who is likely to be at higher risk, and who should pursue these interventions before any sign of bone weakening [2]. A test like this could be an important clinical tool."

Kim is the sole author of the study, which will be published online July 26 in PLOS ONE.

Low bone-mineral density as predictor

Kim originally approached his investigation as a way to help elite athletes or members of the military learn if they are at risk of bone injury during strenuous training. Once he had compiled the results, however, he saw a strong correlation between people predicted to have the highest risk of low bone-mineral density and the development of osteoporosis and fracture.

Osteoporosis, or porous bone, is a disease that results in a reduction in bone mass due to bone loss or defects in bone production, or both. It's correlated with a high incidence of bone fracture because the weakened bone is less able to withstand the stress of slips and falls, or sometimes even normal daily activity. It affects millions of Americans and is responsible for as many as 1 in 2 fractures in women and 1 in 4 in men over the age of 50.

Two previous studies have shown that there is a genetic component to osteoporosis; you're more likely to develop it if you have a family history of the condition. In addition to genetics, your behaviors, including the frequency and type of exercise you prefer and your diet, as well as your weight and gender, also play a large role in bone health [3]. Recently, genetic studies on large groups of individuals have shown that hundreds of genes are likely involved, each making its own small contribution to either increased or decreased risk of the disease.

Osteoporosis is often diagnosed with a bone-mineral density test that uses X-rays to measure the amount of minerals, such as calcium, in a person's hip, spine or heel. But bone-mineral density tests are usually only performed on people with a family history of osteoporosis or those who have experienced a recent fracture from a simple fall.

"The most common clinical algorithm used to detect or predict osteoporosis is called FRAX," Kim said. "But the catch is that the two largest components of the FRAX algorithm are bone-mineral density and prior fracture. So it's kind of a circular argument."

Developing an algorithm

Kim analyzed the genetic data and health information of nearly 400,000 people in the UK Biobank -- a vast compendium of de-identified information freely available to public health researchers around the world. For each participant, Kim collected data on bone-mineral density, age, height, weight and sex, as well that participant's genome sequence [4]. He then developed a computer algorithm to identify naturally occurring genetic differences among people found with low bone-mineral density.

Using the algorithm, Kim was able to identify 1,362 independent differences, or single-nucleotide polymorphisms, that correlated with low bone-mineral density readings. He then used a machine-learning method called LASSO, developed in 1996 by Stanford professor of biomedical data science and of statistics Robert Tibshirani, PhD, to further hone the data [5].

Discussion

The resulting algorithm assigned a score to each of the nearly 400,000 participants to indicate their risk of low bone-mineral density; subsequent analyses showed that those in the bottom 2.2 percent of these scores were 17 times more likely than their peers to have been diagnosed with osteoporosis and nearly twice as likely to have experienced a bone fracture.

Conclusion

"The analysis worked really well," Kim said. "This is one of the largest genomewide association studies ever completed for osteoporosis, and it clearly shows the genetic architecture that underlies this important public health problem."

Kim is now planning to arrange a clinical trial to investigate whether elite athletes and select members of the military identified by the algorithm as being at high risk for osteoporosis and potential fracture can increase their bone-mineral density with simple preventive measures. He's also interested in conducting a similar study among younger people with no obvious clinical symptoms of bone weakening.

"Fifteen million people in this country have already accessed their genome sequences using direct-to-consumer testing services," Kim said. "I think this analysis has the potential to become the standard of care in the coming years. It would be a relatively simple measure to identify those who should have their bone-mineral density tested and perhaps take steps at an early age to ensure their future bone health."

Acknowledgement

None

Conflict of Interest

There is no conflict of interest.

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