Gene variants associated with increased risk of bone fractures, low bone mineral density

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Results from a large study indicate that variants of the gene LRP5 are associated with a significant increase in the risk of fractures, by up to 20 percent, and lower levels of bone mineral density in the spine and hip, according to a study in the March 19 issue of JAMA, a theme issue on *Genetics and Genomics*.

Joyce B. J. van Meurs, Ph.D., of Erasmus MC, Rotterdam, the Netherlands, presented the findings of the study at a JAMA media briefing at the National Press Club in Washington, D.C.

Osteoporosis is characterized by low bone mineral density (BMD), deterioration of bone and increased risk for fractures. Studies have shown that genetic factors determine up to 80 percent of the variance in BMD, which is a major predictor of osteoporotic fractures, according to background information in the article. While the genes that contribute to differences in risk for osteoporosis and osteoporotic fractures are for the most part unknown, it is thought that the risk of developing osteoporosis is dependent on several common gene variants. Variations of the gene LRP5 have been linked to bone mass accrual and susceptibility to osteoporosis, and some reports have suggested that some of these variants contribute to change in BMD in the general population, but results have been inconclusive, partly because of small sample size.

Dr. van Meurs and colleagues examined the association between variants to the genes LRP5 and LRP6 to BMD and risk of fracture using large-scale evidence, with the combined analysis of individual-level data of the

full Genetic Markers for Osteoporosis (GENOMOS) consortium, including data from 37,534 individuals from 18 participating teams in Europe and North America. Bone mineral density was assessed by dual-energy x-ray absorptiometry (an imaging technique). Fractures were identified via questionnaire, medical records, or radiographic documentation; new fracture data were available for some groups, determined via routine surveillance methods, including radiographic examination for vertebral fractures.

“In this large-scale multicenter collaborative study, we obtained evidence that genetic variation of the LRP5 gene is associated with both BMD and fracture risk. The magnitude of the effects was modest but very consistent across studies,” the authors write. “Based on the general acceptance that a 1-standard deviation reduction in bone mass doubles the fracture rate, an increase of fracture risk of about 15 percent to 20 percent is expected. This is similar to the observed effects on fracture, although adjustment for BMD only partly reduced the increase in fracture risk. This could raise the possibility of effects on bone quality, bone dimension, or other nonskeletal determinants of fracture, but also could be due to error in measurement of BMD. Further work will be required to address this point.”

“Our findings demonstrate that the modest effects of common genetic variations in complex diseases can be effectively addressed through large consortia and coordinated, standardized analysis. Such effects might be missed by smaller and potentially underpowered individual studies. This prospective collaborative study with individual level-data of 37,534 participants shows an effect of LRP5 genetic variation on both BMD and risk of fracture. While some other common variants have been associated previously with osteoporosis phenotypes [physical manifestations] with large-scale evidence, this may be the first time that an association in this field crosses the threshold of genome-wide statistical significance.”

“Although the magnitude of the effect was modest, the effect was very consistent in different populations and independent of sex or age. This suggests a role for LRP5 in determining BMD and fracture risk throughout life in the general population. Although any single marker explains only a small portion of the phenotype risk, identification of several such osteoporosis risk variants may eventually help in improving clinical prediction. Single genetic risk variants such as LRP5 may also offer useful insights about mechanisms and pathways that may be useful in drug development,” the researchers conclude.

Source: JAMA and Archives Journals