

# OSTEOSCOOP

News on current events in osteoporosis and rheumatology

## Bone mineral density, osteoporosis, and osteoporotic fractures: a genome-wide association study

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Osteoporosis is diagnosed by the measurement of bone mineral density, which is a highly heritable and multifactorial trait. A recent study [1] aimed to identify genetic loci that are associated with bone mineral density. In this genome-wide association study, the authors identified the most promising of 314 075 single nucleotide polymorphisms (SNPs) in 2094 women in a UK study. They then tested these SNPs for replication in 6463 people from three other cohorts in Western Europe. They also investigated allelic expression in lymphoblast cell lines. They tested the association between the replicated SNPs and osteoporotic fractures with data from two studies.

The authors identified genome-wide evidence for an association between bone mineral density and two SNPs. The SNPs were rs4355801, on chromosome 8, near to the TNFRSF11B (osteoprotegerin) gene, and rs3736228, on chromosome 11 in the LRP5 (lipoprotein-receptor-related protein) gene. A nonsynonymous SNP in the LRP5 gene was associated with decreased bone mineral density and an increased risk of lumbar spine and femoral neck osteoporotic fractures and osteoporosis. Three SNPs near the TNFRSF11B gene were associated with decreased bone mineral density and increased risk of osteoporosis. For carriers of the risk allele at rs4355801, expression of TNFRSF11B in lymphoblast cell lines was halved. 1883 (22%) of 8557 people were at least heterozygous for these risk alleles, and these alleles had a cumulative association with bone mineral density. The presence of both risk alleles increased the risk of osteoporotic fractures and this effect was independent of bone mineral density.

In conclusion, two gene variants of key biological proteins increase the risk of osteoporosis and osteoporotic fracture. The combined effect of these risk alleles on fractures is similar to that of most well-replicated environmental risk factors, and they are present in more than one in five Caucasian women, suggesting a potential role in screening.

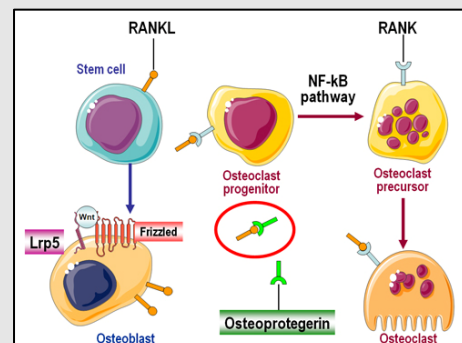
1. Richards JB et al. *Lancet*. 2008;371:1505–1512.

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Osteoprotegerin is a circulating peptide synthesized by osteoblasts. It acts as a decoy receptor of RANK ligand. OPG is therefore a fine tuner of osteoblast-osteoclast cross-talk. The concentration of RANKL and OPG in the plasma of patients can be measured. When synthesis and plasma concentration of osteoprotegerin are decreased, availability of RANK ligand for its receptor RANK is enhanced and osteoclast activation occurs.

Low-density lipoprotein receptor-related protein 5 (Lrp5) is a membrane protein acting as a co-receptor in canonical Wnt signaling. Lrp5 increases osteoblast proliferation, differentiation, and function. Lower synthesis or mutations of Lrp5 lead to a defect in bone formation.

Polymorphisms of osteoprotegerin and Lrp5 are associated with low bone mineral density, osteoporosis and fractures. Since these genetic variants are present in more than one in five white people, they may have a potential role in screening.



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