



GEFOS CONSORTIUM

PRESS RELEASE

Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies

We identified 20 genome regions (loci) robustly associated with bone mineral density (BMD) in individuals of Northern European descent, of which 13 loci are reported for the first time. BMD measured by Dual X-ray Absorptiometry (DXA) is used in clinical practice for the diagnosis and follow-up of patients with osteoporosis. Decreased BMD increases the risk of fracturing bones. The association signals point to genes of diverse types coding not only for skeletal factors but also of muscle. These findings mark a new stage for the understanding of the underlying genetic architecture of osteoporosis by: **1.** underscoring the complexity underlying osteoporosis where dozens and possibly hundreds of genetic variants (in interaction with the environment) influence normal human BMD variation; **2.** confirming the involvement of known bone metabolism pathways like WNT and the RANK-RANKL-OPG signaling in determining BMD; **3.** identifying many novel factors within known and new pathways which by this study have now been implicated in osteoporosis; **4.** showing how these genetic factors decreasing BMD are associated all together with increased risk of fracture (about 5% increased risk of fracture per copy of a risk variant for low BMD).

This study is part of the **GE**netic **F**actors of **OS**teoporosis (**GEFOS**) project sponsored by the European Commission (**FP7-HEALTH- F2-2008-201865-GEFOS**). Additional information on the project can be found at <http://www.gefos.org/>. The objective of GEFOS is to assemble a consortium of genetic studies on osteoporosis that aids the identification of genetic variants associated with the risk of fracture. In osteoporosis as in other complex disorders, huge collaborative efforts are needed to integrate individual research studies into one large study population capable of demonstrating the real, yet very subtle genetic effects underlying such traits. This is the first of such collaborative GEFOS efforts including 19,125 subjects from five population studies from Europe and the US, where 2.5 million markers were analyzed in relation to BMD of the lumbar spine and femoral neck (hip) measured by a technique called DXA.

Given the minor fraction of explained variance in BMD (3%), these genetic factors are not immediately relevant for the diagnosis of osteoporosis or the identification of subjects at risk. Yet, they are very promising findings considering the association of the compound genetic score with the risk of fracture which was observed within the Rotterdam Study (<http://www.epib.nl/research/ergo.htm>) population. This preliminary analysis on fracture showed that carrying one of these “risk” genetic variants increases the risk of fracture similar to what an increase in one year of age does. Considering that at the moment 10 to 15 risk variants for low BMD have been identified for the lumbar spine and femoral neck, respectively, risk differences between individuals with and without the risk variants could be just-as or greater-than the effect exerted by a decade difference in age between extreme groups of individuals. As more genetic variants associated with low BMD are identified the contrast between individuals at risk will increase and potentially gain clinical relevance. It is important that the public is aware that there is no genetic test available suitable for the identification of subjects at risk of developing osteoporosis which performs better than what is done by the joint assessment of clinical risk factors like age, sex, low weight, immobility or history of fracture.

On the shorter term society can benefit from these findings with the development of new compounds for the treatment of osteoporosis derived from the thorough understanding of the identified genes and pathways. Future efforts within the GEFOS consortium will involve meta-analysis of BMD, fracture and other related traits in even larger datasets, as well as follow-up of the identified signals including functionality assessments and fine-mapping of the regions through in-silico and de-novo sequencing.

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