

## Media Release

**Embargoed until 19:00 Central European time/1300 US Eastern time**

**Sunday April 15<sup>th</sup> 2012**

### **Discovery of genes underlying fracture susceptibility and the risk of osteoporosis**

Osteoporosis is a silent but frequent and devastating age-related disease: 50% of subjects that fracture their hip after age 80 years die within 12 months after the event. Actually, women older than 65 years are at greater risk for death after hip fracture than after breast cancer. While the consequences of osteoporosis are well established, the causes of the disease remain elusive. The disease is strongly genetically determined, but the responsible genes are largely unknown. However, this situation has changed dramatically today. According to a study published in the leading genetic journal *Nature Genetics*, variants in 56 regions of the genome have been discovered to influence the Bone Mineral Density (BMD) of individuals. Fourteen of these variants were also found to increase the risk of bone fracture. This is the first time such large number of genetic variants have been robustly found associated with fracture risk.

Bone mineral density measured by Dual X-Ray absorptiometry (DXA) is the most widely used measurement to diagnose osteoporosis and to assess the risk of fracture. In general terms high BMD results in lower risk of fracture. Researchers from the Erasmus University Medical Center in Rotterdam, The Netherlands have led an international consortium of investigators from more than 50 studies across Europe, North America, East Asia and Australia. They have studied more than 80,000 individuals with DXA scans and examined the relation with fracture in approximately 30,000 cases and 100,000 controls, in what constitutes the largest genetic study in osteoporosis performed to date.

“Even though bone mineral density (BMD) has an imperfect relation with fracture risk (i.e., about 50% of individuals without osteoporosis as diagnosed by DXA, however, still suffer fractures), our genetic study on BMD has allowed an unprecedented leap in sheer number of discoveries on human skeletal biology” explains Dr Fernando Rivadeneira, assistant professor in Erasmus MC and lead senior author on the study. “We have now pinpointed many factors in critical molecular pathways which are candidates for therapeutic applications.” he adds. “Such potential is highlighted by the identification (among others) of genes encoding proteins that are currently subject to novel bone medications. This is the case for denosumab (commercial name Prolia), a human monoclonal antibody against RANKL which is a protein inhibiting bone resorption.” Rivadeneira adds: “Yet, even more interesting is the identification of several factors which can constitute targets for true bone-building drugs. This is already the case for the sclerostin gene for which an anti-sclerostin antibody is expected soon to be available in the market.”

This research leads to better understanding of the biology of skeletal health and fracture susceptibility. “In addition, to the known proteins and pathways we have identified we are also confronted with completely new biology”, says Karol Estrada scientific researcher at Erasmus MC and first author of the publication. Estrada adds “There is, for example, very little known about the genomic region on chromosome 18 where we discovered the strongest genetic factor associated with fracture risk. Just less than a month ago the factor underlying the genetic signal was recognized as a gene, now known as FAM210A”.

“We also established that, as compared to women carrying the normal range of genetic factors, women with an excess of BMD-decreasing genetic variants had up to 56% higher risk of having osteoporosis and 60% increased risk for all-types of fractures, adds Douglas Kiel, Professor of Medicine at Harvard University and senior co-author. Even more interesting is our discovery of groups of individuals with a smaller number of variants which protected them against developing osteoporosis or sustaining fractures.

“Using the genome-wide association approach we will continue identifying hundreds of common variants underlying the risk of osteoporosis and fracture,” says André Uitterlinden, Professor of Complex Genetics at Erasmus MC. “Nevertheless, we will need new technologies and approaches to understand more. At Erasmus MC we are now running a whole-exome sequencing project in 3,000 individuals of the Rotterdam Study, which will help us to understand the genetic underpinnings of a complex disease like osteoporosis.”

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**) (<http://www/gefos.org/>). The GEFOS consortium is coordinated at Erasmus MC Rotterdam, The Netherlands.

### Journal Reference:

Karol Estrada et al. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. *Nature Genetics*, 2012; DOI: 10.1038/ng.2249

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