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STUDY IDENTIFIES GENES WHICH INCREASE RISK OF OSTEOPOROSIS AND CONFIRMS POTENTIAL FOR SCREENING

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Issued by Tony Kirby, Press Officer, *The Lancet*

Two genetic variants of key biological proteins have been identified which, when present, increase both the risk of osteoporosis and subsequent osteoporotic fractures. Since these variants are present in more than one in five of the population studied,* there is a potential role for screening. These are the conclusions of authors of an **Article** published early **Online** and in this week's issue of *The Lancet*.

Osteoporosis and its main complication, fragility fractures, cause substantial death and disease globally. The public-health burden of this disease is US$17 billion every year in direct expenditure, a figure expected to increase dramatically as populations age. Osteoporosis is defined clinically through the measurement of bone mineral density (BMD), which remains the single best predictor of osteoporotic fractures. BMD is highly heritable, with estimates of 78% heritability of density at the lumbar spine, and 84% at the femoral neck.

Professor Tim Spector and Dr Brent Richards, Department of Twin Research and Genetic Epidemiology, King's College London, UK and colleagues from the Wellcome Trust Sanger Institute, UK, and Rotterdam did a genome-wide association study† 2094 female twins and identified the most promising single nucleotide polymorphisms‡ (SNPs) in their genes, from a total of 314 075 possibilities, which could be responsible for conferring a higher risk of osteoporosis. To confirm this, they then tested these SNPs in 6463 people from three other studies in Western Europe.

They identified evidence for an association between BMD and two SNPs—in chromosomes 8 and 11. In chromosome 11, the SNP was on the *LRP5* (lipoprotein-receptor-related protein) gene,§ and a variant SNP here was associated with decreased BMD and a 30% increased risk of both osteoporosis and osteoporotic fractures. In chromosome 8, the SNP was close to the *TNFRSF11B* (osteoprotegerin) gene,§ and a variant here was found to decrease BMD, and increase the risk of osteoporosis by 20%. In the 22% of people who carried both of these

risk variants (ie, had both risk alleles¶), the risk of osteoporotic fractures was increased by 30%—and this effect was independent of BMD. Both these genes are important targets for bone therapies and drugs are already in development.

The authors say: "These alleles can be measured with near-perfect precision and without bias years before the age at which fractures tend to occur—which could provide ample lead-time for preventive measures. Eventually, a panel of genetic markers could be used in addition to environmental risk factors to identify individuals who are most at risk for osteoporotic fractures."

They conclude: "We have identified genetic variants that decrease bone mineral density and predispose people to osteoporosis and osteoporotic fracture. The increase risk of osteoporotic fracture in people who had both risk alleles was independent of the affect of these alleles on BMD...The combined effect of these risk alleles on fractures is similar to that of most well-replicated environmental factors, and they are present in more than one in five white people, suggesting a potential role in screening."

In an accompanying **Comment**, Dr Joseph Zmuda, D and Dr Candace Kammerer, Graduate School of Public Health, University of Pittsburgh, PA, USA, describe the report as an important step forward toward understanding the genetic basis of osteoporosis. They say that follow-up studies are necessary to identify the genetic mechanisms involved, and, since the paper focuses on mostly white women of European descent, studies of the effects of these two SNPs will need to be done in other populations.

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Note to Editors

*The population studied was white European. This is because North European whites are the highest risk group in the world for fractures—especially females. Also, for genetic studies to discover genes it is necessary to use homogenous similar populations.

†Genome-wide association study: an unbiased way of seeking associations between genes and diseases by studying large groups of people, some who have the disease, and some who do not, using large number of gene markers spread throughout the gene.

‡Single nucleotide polymorphism: the DNA in chromosomes is made up of a long double-helix of two chains of molecules called nucleic acid bases, adenine, guanine, thymine, and cytosine (A,G,T, and C). An SNP is when there is a change in one of these bases in the chain between two individuals in the same species.

§Both the *LRP5* and *TNFRSF11B* (osteoprotegenin) genes are involved in bone metabolism, and drugs are in development using their mechanisms for osteoporosis treatments.

¶Allele: consider two sequenced DNA fragments from different individuals, AAGC**C**TA and AAGC**T**TA, that contain a difference in a single nucleotide as shown. In this case we say that there are two alleles : C and T.

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