



## Genome-Wide Association Study (GWAS) of Osteoporosis in US Caucasians

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### Background and hypothesis

GWAS are increasingly utilized for the complex diseases, such as diabetes, cancer, and obesity. These studies include large arrays of hundreds of thousand single nucleotide polymorphisms (SNPs) and employ hypothesis-free strategies. Since osteoporosis is a heritable disease, we have undertaken a GWAS to localize susceptibility genes for osteoporosis-related traits from the Framingham Heart Study.

### Methods

Osteoporosis-related traits included femoral neck and lumbar spine bone density and proximal femoral geometry (measured by DXA). An Affymetrix 550K SNPs panel was used, with 433,510 SNPs that passed initial quality control using rigorous criteria (call rate  $\geq 95\%$ , Hardy-Weinberg Equilibrium test  $p \geq 10^{-6}$  and Minor allele frequency  $\geq 0.01$ ) in 2,005 women and 1,496 men (mean age 62.5 yrs) from 677 extended pedigrees. We conducted population- and family-based analyses. Sex-specific residual trait values with adjustment for age, height, BMI, and menopause status (women) were used. A principle component analysis was performed to model differences of individuals' ancestral genetic background. The first 4 principle components (PCs) were significantly associated with bone traits, indicating that population substructure exists in our sample. To minimize spurious associations, we adjusted for these PCs in linear-mixed effects regression models that fully account for correlations within families.

### Results

Several associations achieved genome-wide significance level, i.e. SNPs near/within BMP10, PTPRD, MYC, SLC16A4, IL6 and PRKG1 genes. To test whether associated genes are expressed in bone, we examined a mouse gene expression database using mRNA from PTH-differentiated primary osteoblasts. All the above genes except BMP10 and MYC were expressed in stimulated osteoblasts. The 2,500-3,000 most significant SNPs from each trait (at  $p < 10^{-3}$ ) are being further evaluated, at the present, in ~2,650 men and 5,850 women from 2 independent studies.

### Conclusions

Novel technological and analytical developments that make the GWAS in FHS possible, offer an unbiased genome-wide strategy to detect novel genetic associations and to select promising loci for further functional study. GWAS are laying the groundwork for personalized medicine in osteoporosis and other common diseases.