The influence of GWAS-based gene variants on the bone-remodelling marker Osteocalcin in the Gene SMART study

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Introduction: Bone remodelling is tightly controlled by osteoclasts and osteoblasts that balance bone removal and bone formation, ultimately determining bone mineral density (BMD). This process is difficult to assess therefore circulating bone remodelling markers (BRM) such as Osteocalcin (OC) are commonly used as a surrogate measure. BMD is highly heritable with some estimates reaching 84%. The aim of this study was to determine whether genetic variants associated with bone health in Genome Wide Association Studies (GWAS), are associated with circulating levels of OC.

Methods: We measured levels of total OC (tOC), and carboxylated OC (cOC) in blood of 73 healthy Caucasian males from the Gene Skeletal Muscle Adaptive Response to Training (SMART) study. We also genotyped those 73 men for 14 genetic variants known to be associated with broadband ultrasound attenuation (BUA) and/or velocity of sound (VOS) that estimate bone structure and fragility, from a published GWAS (Moayyeri *et al.*, 2014). We calculated two genetic Risk Score (GRS) based on those 14 variants and performed linear regressions after adjusting for age, to test whether the two GRS were associated with tOC, or cOC.

Results: The VOS-based GRS was associated with higher tOC levels (B=0.168; *P*=0.029; 95% CI 0.018, 0.317) and higher cOC levels (B=0.196; *P*=0.038; 95% CI 0.011, 0.380). The BUA-based GRS was also associated with higher tOC (B=0.186; *P*=0.037; 95% CI 0.012, 0.361) and higher cOC (B=0.224; *P*=0.038; 95% CI 0.012, 0.435).

Conclusion: In summary, we found that regardless of age, individuals who have a higher GRS for bone structure and fragility also have increased circulating levels of tOC and cOC. This study may lead to better identification of people at risk for osteoporosis or other bone disorders.

Moayyeri A, Hsu YH, Karasik D, Estrada K, Xiao SM, Nielson C, Srikanth P, *et al.* (2014). Genetic determinants of heel bone properties: genome-wide association meta-analysis and replication in the GEFOS/ GENOMOS consortium. *Hum Mol Genet* **23(11)**, 3054-3068.