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Vitamin D receptor haplotypes and fracture risk

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Vitamin D plays an essential role in skeletal metabolism by binding to its nuclear steroid receptor, the vitamin D receptor (VDR). The heritability of bone mineral density (BMD) is well established, and the *VDR* gene is considered a prime candidate suggested to partially account for genetically controlled BMD variance in the population. The aim of a recent study was to reconstruct common haplotypes in the *VDR* 3' untranslated region (UTR) and studied the association to BMD and risk of vertebral fractures in 3014 elderly men from Sweden and 2000 in Hong Kong, all participants of the global MrOS Study. To assess any functional implications of the VDR polymorphisms, the authors studied allele-specific expressions of the different VDR 3' UTR haplotypes in the normal chromosomal context of 70 unrelated human trabecular bone samples. This was performed by quantitative genotyping of coding polymorphisms in RNA samples and in corresponding DNA samples isolated from the bone samples.

Three major haplotypes were reconstructed and in agreement with the previously well-defined *baT*, *BAt*, and *bAT* haplotypes, herein denoted *Hap1*, *Hap2,* and *Hap3*. The *Hap1* haplotype was independently associated with increased risk of vertebral fractures in Swedish men (OR, 1.655; *P* <0.01) and with lower lumbar spine BMD in elderly men from Sweden (*P* <0.01) and Hong Kong (P <0.05). The *VDR* gene was also shown to exhibit a 3' UTR haplotype dependent allelic imbalance, indicating that the VDR *Hap1* allele was overexpressed in human trabecular bone samples.

These results indicate that the relatively overexpressed VDR *Hap1* haplotype could be considered a risk allele for osteoporosis regardless of ethnicity.

1. Grundberg E et al. *J Bone Miner Res.* 2007;22: 832–840.

Vitamin D receptor haplotypes and the fracture risk

Vitamin D acts on the intestine, where it stimulates calcium and phosphate absorption, and on bone cells through its receptor (VDR). Three major haplotypes were reconstructed in the 3' untranslated region (UTR) of the vitamin D receptor. One of them is associated with increased risk of vertebral fractures and with lower lumbar spine BMD in elderly men.

These results indicate that the relatively overexpressed VDR *Hap1* haplotype could be considered a risk allele for osteoporosis.