

Qiuju Huang
Dr. med.

A population-based association between genetic markers and osteoporosis

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Doktorvater: Priv.-Doz. Dr. med. T. Schilling

The risk of osteoporosis is solely attributable to fracture. The bone mineral density (BMD) as a surrogate measure of bone mass is an established predictor for osteoporotic fractures. To determine genetic effect on the pathogenesis of osteoporosis, we specifically chose to examine the previously widely studied restriction fragment length polymorphisms (RFLPs). We utilized a direct haplotyping method to examine the three polymorphic sites (BsmI, ApaI and TaqI) of VDR gene and two polymorphic sites (PvuII and XbaI) of ER gene. More, the FokI polymorphism of VDR gene and the Sp1 polymorphism of COLIA1 gene have been genotyped. In the study, we analyzed the association of these common RFLPs to BMD and bone loss within a population-based sample of 50-80 year old Caucasian men and women. We also determined the role of the common RFLPs as risk factor for primary manifest osteoporosis with at least one fracture.

Among 157 men and 128 women, the results show that the 'bb' genotype of VDR gene was related with low femoral neck BMD among women, and great bone loss at femoral neck among men. Although there was no statistical association between BMD or rate of bone loss across different genotypes by haplotyping, the haplotyping enables a more precise identification than individuals at high risk of low BMD. Multiple linear regression analysis shows the significant effect for the 'bb' genotype combination with calcium intake or exercise on male bone mass. While there are the significant interactions between 'bb' genotype and physical activity, menopause age and HRT on bone mass among women. Analyzed FokI genotypes of VDR gene, we found the 'ff' genotype was related with great bone loss among women. Similar results to VDR haplotyping, the ER gene haplotyping shows more precise identification individuals at high risk of low BMD, although there was no statistical association across the different genotypes. We did not observed any association between COLIA1-Sp1 polymorphism and BMD or BMD change.

Compared 189 of primary manifest osteoporotic cases (69 men and 120 women) with 201 controls (131 men and 70 women), we did not found any overexpression in VDR-BsmI and

FokI polymorphisms, ER-XbaI and PvuII polymorphisms, and COLIA1-Sp1 polymorphism, respectively. When stratified the cases by decades of age at diagnosis, the frequencies of 's' allele in COLIA1 gene showed a significant linear trend to increase across strata from lowest to highest age at diagnosis in women.

Our results are consistent with some previous studies, but inconsistent with others. Heterogeneity in the genetic background on these gene loci among different populations might explain for varying study results. Another possible explanation is that these gene alleles may not directly influence BMD but may be in linkage disequilibrium with a causal gene locus nearby that influence BMD. Alternatively, gene-environment interaction is potential explanation for the discrepancies seen between studies.

In conclusion, our observations support the view that the VDR gene BsmI or FokI polymorphisms have effect on BMD and BMD change, but not on clinical significance. It might act as a risk modifier rather than as a major risk factor of osteoporosis. The PvuII and XbaI polymorphisms in ER gene may not contribute to bone mass and are unlikely to be of clinical value in identifying subjects who are at risk for osteoporotic fracture in our study population. The Sp1 polymorphism in COLIA1 gene may have a clinical significance as a risk factor of osteoporotic fracture in elder women. In order to identify such interaction effects and to estimate their public health impact, there is need for large population-based case-control and cohort studies. The polymorphism of the VDR, ER and COLIA1 genes would be just small part of several possible genetic susceptibility factors to be considered. Environmental interventions, such as greater calcium intake or higher level physical activity, may also be important for the prevention of osteoporosis.