PP277

A genomic and transcriptomic approach to the high bone mass phenotype: evidences of heterogeneity and of additive effects of *TWIST1*, *IL6R*, *DLX3* and *PPARG*

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INTRODUCTION

High bone mass (HBM) was defined as an asymptomatic autosomal dominant condition characterized by increased bone mineral density (BMD) due to gain-of-function mutations in the *LRP5* gene. In the general population, BMD is normally distributed, and at the high extreme of the curve people display BMD values similar to those found in HBM patients (Fig. 1).

The range of densities of HBM is defined by:

(LS Z score + Hip Z score) > 4

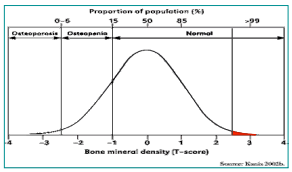


FIGURE 1. Distribution of BMD in healthy women aged 30-40 years. Values similar to HBM patiens are highlighted in red. (Adapted from Kanis 2002)

OBJECTIVES

- To establish the prevalence of the high bone mass phenotype in the BARCOS cohort of postmenopausal Spanish women
- To determine whether any of the HMB cases carry *LRP5* or *DKK1* mutations that explain the phenotype
- To test the hypothesis of an inverse correlation between the number of common variant osteoporosis risk alleles and HBM
- To characterize the expression pattern of osteoblast-specific and Wnt pathway genes in primary osteoblast RNA samples from two HBM cases

RESULTS

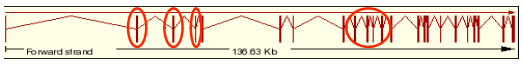
➢ Prevalence of HBM in the BARCOS cohort = 0.6%

TABLE 1. Total Sum Z-score values.

Probands (BARCOS)	Sum Z-score
HBM1	6.1
HBM2	4.6
HBM3	4.9
HBM4	4.5
HBM5	4.5
HBM6	5.1
HBM7	4.6
HBM8	7.9
HBM9	7.0
HBM10	5.1
Additional probands	**Sum Z-score**
HBM11	6.8
HBM12	6.4
HBM13	5.2
HBM14	6.0
HBM15	4.5
HBM16	5.3

➢ No mutations in the analysed exons of the *LRP5* gene (Fig. 2) were found in these patients.

➢ One patient carried a missense change in the *DKK1* gene.



LRP5.

FIGURE 2. Diagram of *LRP5* (23 exons). Marked in red are those exons of *LRP5* that were analyzed.

➢Regarding the risk allele analysis, results point to an inverse correlation between these and BMD in the HBM group of women, although a woman with one of the highest BMD values presented with one of the highest risk score. A low frequency penetrant unknown genetic variant could be a possible explanation for this case (Fig. 3).

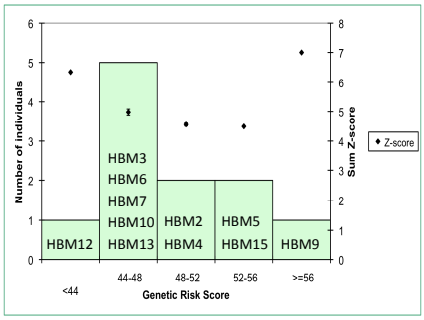
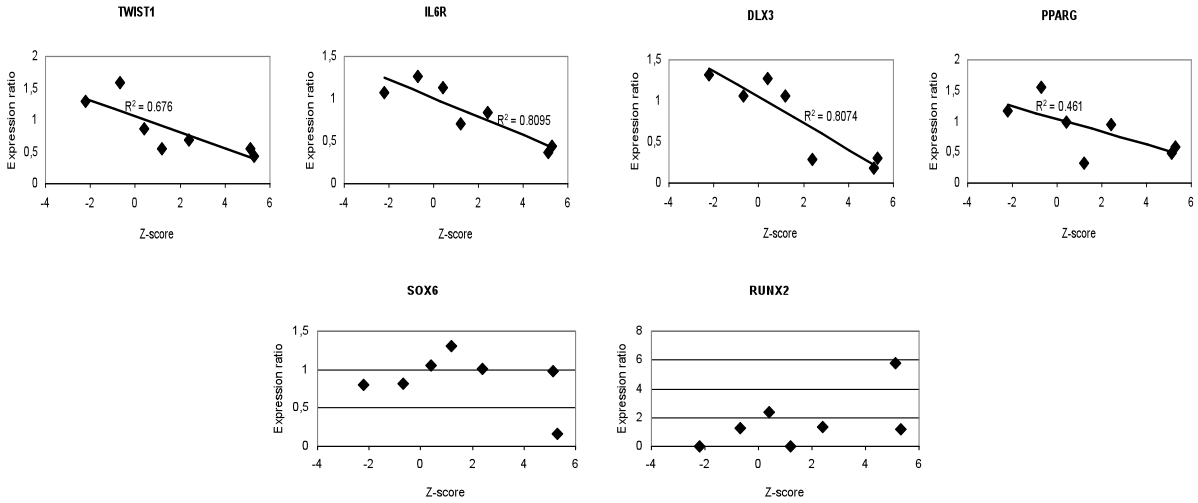


FIGURE 3. Eleven HBM cases were genotyped for 55 BMD *loci*, distributed in risk-score bins and plotted against sum Z-scores as in Estrada *et al*. (Nat Genet. 44:491-501,2012)

➢ The expression analysis showed that six genes could be involved in the generation of the HBM phenotype: *TWIST1*, *IL6R*, *DLX3*, *PPARG*, *RUNX2*, and *SOX6*.



CONCLUSION

- *LRP5* does not seem to be the cause of the HBM phenotype in these cases from BARCOS cohort.
- The BMD risk allele analysis showed an inverse correlation with BMD in the HBM group.
- The results of the expression study raise new hypotheses that should be further investigated.

The authors declare no conflict of interest