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Genome-wide haplotype association mapping in mice identifies a genetic variant in CER1 associated with bone mineral density and fracture in southern Chinese women.

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Introduction: Osteoporosis is characterized by a decrease in bone mass, deterioration of bone tissue, impaired bone strength and increased fracture risk. It is a medically, socially, and economically important disease, especially among the aging population. Bone Mass Density (BMD) is a quantitative index of osteoporosis. Acquisition of bone mineral is a complex process involving genetics and environmental factors. **Methods:** A genome-wide Haplotype Association Mapping (HAM) approach was performed by using inbred mice strains which had been genotyped and phenotyped in the Mouse Phenome Project. In HAM, a dense SNPs map was first partitioned into blocks of three SNPs with an average length of 1Mb. Modified F-statistics were calculated for the whole genome to test if blocks exist where the haplotypes can partition inbred strains into high and low BMD groups. In this study, the candidate gene Cerberus 1 (Cer1) suggested from HAM analysis was eventually tested by a human case-control cohort of 1,083 subjects. **Results and conclusion:** In this study, we used a HAM approach to identify a haplotype block within Cer1 that partitions inbred mice strains into high and low BMD groups. A cohort of 1083 high and low BMD human subjects were studied and a non-synonymous SNP (rs3747532) in human CER1 was identified to be associated with increased risk of both low BMD in premenopausal women (OR 2.2; 95% confidence interval: 1.0 - 4.6; $p < 0.05$) and increased risk of vertebral fractures (OR 1.82, p=0.025) in the post-menopausal cohort. We also showed that Cer1 is expressed in mouse bone and growth plate by RT-PCR, immunohistochemistry and in situ hybridization, consistent with polymorphisms potentially influencing bone mineral density. Our successful identification of an association with CER1 in humans together with our mouse study suggests that CER1 may play a role in the development of bone or its metabolism.