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# Is skeletal mechanotransduction under genetic control ?

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**Abstract**

Studies of twins have established that peak bone mass is about 70% heritable. The skeletal response to exercise contributes to peak bone mass, as mechanical loading increases skeletal mass during growth and development. It is possible that the skeletal responsiveness to mechanical loading is under genetic control, so that some individuals will build stronger bones with exercise. This appears to be the case in mice. Long bones in mice of the C3H/He strain are largely unresponsive to mechanical loading. Ironically, this strain of mice has very high bone density. Perhaps the genes that regulate BMD are not the same as those that regulate mechanical loading response. Studies of recombinant inbred and congenic strains derived from C3H mice will help to identify genes influencing bone size, density and responsiveness to mechanical loading.

**Keywords:** Bone Density, Mice, Genetics

## Introduction

The lack of mechanical usage during growth impairs the development of a long bone's characteristic cross-section. For instance, an immobilized femur will develop with a fairly round cross-section, rather than the typical elliptical shape. Bone adaptation is generally considered an epigenetic phenomenon, however this view is being challenged by recent studies in mice. The high bone mass C3H/HeJ (C3H) strain of mice has long bones that are largely unresponsive to mechanical loading[1,2]. Interestingly, a tibia of a C3H mouse has a rounded cross-sectional shape, rather than the more triangular shape seen in mice from the C57BL/6J (B6) strain. The rounded C3H tibia resembles a rat's tibia that developed without mechanical loading[3], suggesting that the C3H tibia did not adapt its shape to loading patterns during growth. We hypothesize that a mechanosensitivity gene exists with active alleles in B6 and inactive alleles in C3H. Consequently, these genetic alleles would be transferred to offspring. In the present study, we evaluated the femoral cross-sectional moment of inertia (CSMI) and bone mineral density (BMD) in 12 BXH recombinant inbred (RI) mouse strains. Each RI strain contains a unique combination of B6 and C3H alleles. We used the CSMI as a surrogate for the mechanosensitivity of the femoral cortex: a larger CSMI reflects a more elliptical shape which presumably represents greater mechanical adaptation. If mechanosensitivity genes exist, some of the RI strains will be homozygous for active B6 alleles and should have high CSMI values. Those RI strains homozygous for inactive C3H mechanosensitivity alleles should have low CSMI values.

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## Materials and methods

The study involved twelve BXH RI strains of mice and the progenitor strains C3H and B6 (N=7-13). All mice used in the study were female and 8 months old. Isolated femurs were scanned at 2 mm intervals using peripheral quantitative computed tomography to determine femoral BMD and cortical thickness at the femoral midshaft. The CSMI in the mediolateral direction was calculated as

$$CSMI = \pi/64 * a^3b - (a-2t)^3(b-2t) \quad (1)$$

where a is the femoral width in the mediolateral direction, b is the femoral width in the anteroposterior direction, and t is the average cortical thickness. Comparisons among the BXH RI strains and the progenitor strains, B6 and C3H, were done using ANOVA, with Fisher's least significant difference tests for posthoc group comparisons.

## Results

Of the 12 BXH RI strains, only results from 11 are reported. Mice from the BXH-2 strain developed early onset leukemia and were excluded from the study. C3H mice had 48% greater femoral BMD compared to B6 mice. All BXH RI strains fell between both progenitor strains in femoral BMD. Among the BXH strains, BXH-14 had the highest femoral BMD, yet it was significantly less than that of C3H, and BXH-3 had the lowest femoral BMD which was significantly greater than that of B6.

The B6 femur had an elliptical cross-section that was elongated in the mediolateral direction. Conversely, the C3H/HeJ (C3H) femur had a fairly round cross-section with significantly less width in the mediolateral direction and more width in the anterioposterior direction. Due to the elongated M-L width, the femoral CSMI was 35% greater for B6 mice compared to C3H mice ($p<0.0001$). BXH RI strains tended to segregate into either B6-like or C3H-like categories (Figure 1). CSMI was not correlated with femoral BMD ($p>0.15$) among the different strains.

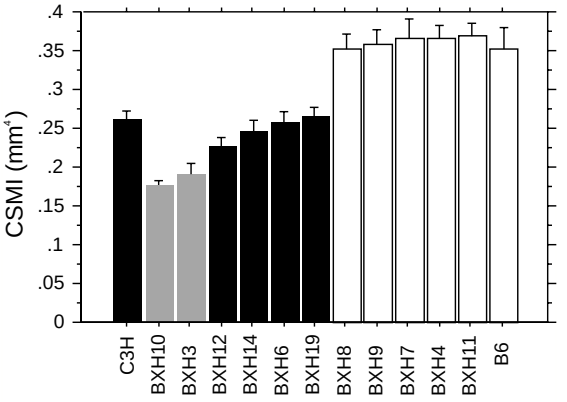


**Figure 1.** White bars indicate strains that were significantly different from C3H, but not significantly different from B6. Black bars indicate strains that were significantly different from B6, but not significantly different from C3H. Striped bars indicate strains that were significantly different from both B6 and C3H.

## Discussion and conclusions

The C3H femur has a fairly round cross-section compared to the elliptical shape of the B6 femur suggesting impaired mechanical adaptation during growth. It appeared therefore that the B6 mice possessed a key skeletal mechanosensitivity gene(s) with significantly greater activity than that in the C3H mice. There was no correlation between CSMI and femoral BMD, suggesting that the genetic influence on femoral shape was independent of any influence on femoral density.

The pattern of larger B6-like CSMI present in five (44%) BXH RI strains, lower C3H-like CSMI present in four BXH RI strains, and very low CSMI present in two BXH RI strains suggests that there may be a single strong effect gene and a modifier gene that controls femoral cross-sectional shape in the B6 and C3H progenitor strains. When the C3H alleles of the primary gene are present, the femur adapts poorly to M-L bending forces. Since two RI strains had lower CSMI values than even C3H, this suggests that both B6 and C3H alleles at the modifier gene locus reduce responses to M-L forces.

## References

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