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Heritability of lumbar trabecular bone mechanical properties in baboons

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Studies of bone mineral density (BMD) consistently demonstrate that this trait has a strong genetic component[1-3]; however, it is well accepted that BMD only partially explains bone strength[4-6]. Bone mechanical properties provide a more direct, inclusive measure of bone's fracture resistance. A genetic effect on mechanical properties has been demonstrated in rodents[7-10] but not in primates and the degree to which these genetic effects contribute to normal population level variation in mechanical properties has not been determined.

Substantial differences in fracture properties between primate and non-primate species[11] underscore the need for a genetically well-characterized non-human primate model to assess the genetics of bone mechanical properties. The baboon shares physiological and developmental characteristics with humans that makes it particularly well-suited to skeletal studies. Statistical genetic analyses of areal bone mineral density and serum markers of bone turnover in the pedigreed baboons from the Southwest Foundation for Biomedical Research/Southwest National Primate Research Center (SFBR/SNPRC) have shown that a significant proportion of the variation in these phenotypes is heritable in this non-human primate[12-15]. These studies have also led to the localization of quantitative trait loci (QTLs) for these traits, some of which provide cross-species replication of QTLs in humans, and some of which are novel[12,13,15].

The specific aims of the study reported here are to: 1) characterize normal variation, including age and sex effects, on vertebral trabecular bone mechanical properties in the baboon; and 2) detect and quantify the proportion of variation in vertebral trabecular bone mechanical properties that is due to the additive effects of genes (heritability (h^2)). The sample of 156 baboons includes 110 females and 46 males (6-32 years) from a single extended pedigree. Bones were collected at necropsy and placed in frozen storage prior to sample preparation. Cranio-caudally oriented trabecular bone cores (6 mm in height, 9 mm in diameter) were obtained from the third lumbar vertebral body. Cores were scanned using microCT (uCT-20; SCANCO USA, Inc.) to obtain cross-sectional area (CSA, mm^2), bone area, and bone volume/tissue volume. Cores were tested to failure in monotonic compression using a servohydraulic testing machine (Model 858 Mini Bionix II, MTS Corp., Minneapolis, MN). Ultimate stress, modulus, and toughness were determined from load vs. displacement data (10 Hz). Age, sex, and additive genetic effects were assessed using maximum likelihood-based variance components methods implemented in SOLAR[16].

After accounting for relatively small but significant age and sex effects, a substantial amount of the residual variation in ultimate stress (0.58 ± 0.20; $p=0.0005$), modulus (0.29 ± 0.24; $p=0.0855$) and toughness (0.64 ± 0.22; $p=0.0003$) is attributable to genes. Subsequent analyses that control for bone volume ($h^2=0.55\pm0.20$; $p=0.0009$) yield non-significant heritability estimates for ultimate stress (0.15 ± 0.14; $p=0.1042$) and modulus (0.02 ± 0.13; $p=0.4413$), suggesting that much of the genetic effect detected in the first analyses acts through bone volume. Interestingly, the results for toughness differ. When bone volume is accounted for a significant genetic effect on toughness (0.29 ± 0.23; $p=0.0389$) remains, indicating that variation in toughness is due, in part, to genes that affect bone volume, but that nearly a third of the genetic variance is due to genetic effects that are independent of bone volume.

These results clearly demonstrate that mechanical properties of trabecular bone of the spine are strongly heritable in this non-human primate model. In addition, the results strongly suggest that these genetic effects are largely, but not

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entirely, due to genetic effects on trabecular bone volume. In contrast to ultimate stress and modulus, a substantial portion of the genetic variance in toughness appears to be due to a gene or set of genes that act on contributors to bone fracture resistance that are independent of bone volume.

Complementary ongoing research

As a critical complement to the results presented here, a similar study involving cortical bone mechanical properties using the femurs from the same animals is in progress. The cortical bone study also involves data on cortical bone microstructure (osteon size, Haversian canal size, porosity, osteon population density) and ash fraction.

If, as expected, these properties show significant genetic effects, the next step is to expand the sample to the larger number (~600 animals) required for genome-wide linkage screens to identify the chromosomal regions that influence bone quality. Together these data will comprise an unmatched resource for a comprehensive investigation of the genetic architecture of multiple contributors to normal variation in bone fracture resistance. Because these data all derive from the same animals in a powerful extended pedigree configuration, they will allow for identification of pleiotropic genetic networks (chromosomal regions harboring genes that affect bone quality in ways that are evident via multiple phenotypes and/or skeletal sites). These analyses will enable the mapping of genes that have significant effects on variation in multiple measures of bone quality and, subsequently, identify candidate genes with the greatest potential for exerting the strongest effects on bone fracture resistance. In the long term, identification of such genes may shed light on the most important pathways for pathogenic mechanisms and have profound implications for identifying those individuals at greatest risk for fracture, and for choosing courses of treatment in high-risk individuals.

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