

Award # 49357

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Ian J. Wallace: Genotyp-specific Growth Patterns and Long bone Functional Adaptation

Limb bone structure is often used to infer hominin activity levels from skeletal remains, an approach based on bone's ability to adjust to its loading environment during life. However, bone structure is also influenced by genetic factors, which has caused some to question its utility for reconstructing past activity. Given the influence of genetics on bone structure, two questions needed to be addressed for functional interpretations of hominin limb bones to be justified. First, is the genetic variation underlying bone structure influenced by the activity levels of *ancestral* populations? If so, then genetic variation in bone structure would have functional significance in an evolutionary context. Second, to what degree does genetic background influence how sensitive bone is to loading? If an interaction between genetic background and mechanosensitivity exists, then the use of bone structure for making inferences about activity levels would need to be re-assessed. The goal of this project was to address these questions by adopting an experimental approach utilizing the mouse model.

To examine the degree to which limb bone structure reflects the activity levels of members of a lineage, my coworkers and I used microcomputed tomography to test for differences in femoral diaphyseal structure in one-week-old mice from a line that had been artificially selected for 45 generations for high voluntary wheel running and non-selected controls. As adults, selected mice are significantly more active on wheels and in home cages, and have thicker diaphyses. Structural differences at one week were assumed to primarily reflect the effects of selective breeding for high activity rather than functional loading, given that the onset of locomotion in mice is shortly after day seven. We hypothesized that if genetic variation in bone structure reflects the activity levels of members of a lineage, then selected mice will have relatively larger diaphyses at one week compared to controls. The results provided strong support for this hypothesis and suggested that limb bone structure may not always reflect the activity levels of particular fossil individuals, but nevertheless conveys an evolutionary signal providing information about hominin activities in the past. These findings were presented at the 2010 meeting of the American Association of Physical Anthropologists¹ and published in the American Journal of Physical Anthropology².

To examine the degree to which mechanosensitivity is influenced by genetic background, my coworkers and I are currently in the process of using microcomputed tomography to measure trabecular bone structure in the distal femora of four replicate lines of mice artificially selected for high wheel running for 21 generations and in four non-selected control lines. Mice from each of the eight lines were housed either with or without wheel access for two months starting at 25-28 days of age. At present, the bones have all been scanned, but the structural parameters have

not yet been computed. This will be completed in the next few months, and then structural parameters will be analyzed by two-way analysis of variance to test for interactions between the effects of genetic background (selected vs. control lines) and activity (sedentary vs. active). Our findings will again be submitted to the American Journal of Physical Anthropology.

A small side project investigating the interaction of bone and muscle in mice from the selection experiment for high wheel running behavior was also made possible by the grant. The influence of muscle on bone structure is an issue that has long been of interest to anthropologists. Over the course of the selection experiment, a recessive allele, named MM, was identified in three lines of mice that halves hind limb muscle mass. Mice with the MM allele also have reduced hind limb diaphyseal dimensions. However, it was unclear whether slender diaphyses are a pleiotropic effect of the MM allele or an epigenetic phenomenon related to the interaction of bone and muscle. To examine this issue, my colleagues and I tested for differences in diaphyseal structure in one-week-old mice from a MM line and two non-MM lines. We reasoned that slender diaphyses among MM mice at this age would suggest a pleiotropic effect because differences in muscle mass are not yet observable at one week postnatal. The results of this study will be presented at the upcoming meeting of the Society for Integrative and Comparative Biology in January 2011.

In sum, as a result of the financial support of the Leakey Foundation, my coworkers and I were able to investigate two issues that are critical to functional interpretations of hominin bone structure. Our efforts have already resulted in publications^{1,2}, and additional publications will be forthcoming. We were also able to complete a side project, which will be of interest to certain anthropologists. Thank you for making this research possible.

References

1 Wallace IJ, Middleton KM, Lublinsky S, Kelly SA, Judex S, Garland T Jr, Demes B. 2010. Activity, genes and diaphyseal structure. *Am J Phys Anthropol Suppl* 50:238.

2 Wallace IJ, Middleton KM, Lublinsky S, Kelly SA, Judex S, Garland T Jr, Demes B. 2010. Functional significance of genetic variation underlying limb bone diaphyseal structure. *Am J Phys Anthropol* DOI 10.1002/ajpa. 21286.