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System level genes or physiological adaptation?★,,★,,★

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Harold Frost's mechanostat model [1], which formalizes Wolff's law of skeletal adaptation, has served as a critical organizing framework for understanding the physiology of skeletal responses to mechanical loading. The model predicts that bone senses and adapts to its mechanical environment, so that underloaded bones lose mass, as in prolonged bed rest or space flight, while overloaded bones gain mass, as in elite racquet sport athletes. This framework has been enormously fruitful, stimulating research by many labs to identify the molecular components necessary for mechanostat function. Further, it motivated development of various experimental skeletal loading and unloading systems that have allowed rigorous and controlled testing of the candidate molecules in model organisms. Together, these efforts have accounted for a large segment of the last generation's considerable progress in skeletal biology.

Parallel efforts have sought to define the genetic basis of fracture susceptibility, and this work has also been informed by the mechanostat model, with structural and biomechanical traits now being routinely included in most model organism studies and structural traits being included in many human investigations. A recurring theme of work in rodents, which has been more extensive and detailed than in any other system, is that many genetic loci appear to affect multiple bone traits, not just one [2]. Understanding this phenomenon, known as pleiotropy, is one of the outstanding challenges of quantitative trait genetics, and exists in many domains outside of bone biology.

In prior work [3], Jepsen and colleagues have modeled the alternative methods by which femora can adapt to maintain stiffness, or the amount of bending imparted to a bone in response to a given force. Stiffness can be achieved in any of several ways. The bone can model, and stiffness arises as a result of a greater diameter and therefore a greater moment of inertia. The cortex may thicken, resulting in both a greater cross-sectional area and a greater moment of inertia. Finally, the cortex may achieve a greater mineralization, with additional stiffness arising as a result of tissue composition rather than geometry. Using this conceptualization, they have developed descriptive equations that relate these 3 properties of

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long bones to each other, in effect defining a mathematical space of physiologically appropriate solutions to the ambient loading environment.

In this issue, Smith et al. [4] report on the skeletal phenotypes of chromosome substitution mouse strains. These strains were bred by selective breeding to allow each mouse autosome to be transferred from A/J to C57BL/6J. In this manner, the substituted chromosome is placed in the context of the C57BL/6J genome. The principal findings of their paper are that 14 chromosome substitutions result in changes to femoral structure, mineralization, or mechanical performance. Half of these affect femoral structure or mineralization without changing mechanical performance, 6 show alterations of both structure and performance, and in a single case, the substitution impairs biomechanical performance without altering structure or mineralization. These are important findings, highlighting the robustness of the femur's capacity to compensate for allelic variation so as to maintain biomechanical performance.

The authors interpret their data as evidence that the allelic variations arising from chromosome substitution act not on individual traits, but on an integrated system. Thus, in their view, it is counterproductive to consider any particular trait of their model's trio as primary, but these should instead be considered jointly. While this is a legitimate inference from their data, it is not the only tenable one. Most genes encode, and so affect, the structure or expression of a single protein. There is a great deal of biology that intervenes between the expression of a single protein and the ways in which cells, tissues, organs, organ systems, and individuals can buffer the impact of a change in a protein's expression. Understanding that biology in detail is bound to improve our insight into skeletal homeostasis, and offers the possibility that a “primary” skeletal trait can be identified in the face of pleiotropy. Another important consideration is that chromosome substitution entails many allelic changes, and the present study does not address how many allelic differences contribute to the differences in femoral morphology, mineralization, and mechanical performance observed in these mice. It is important to note that genetic fine mapping experiments have revealed that various apparently pleiotropic quantitative trait loci (QTLs) can be resolved into a series of closely linked, distinct genes displaying much less pleiotropy. Thus, skeletal QTLs may prove to be analogous to the major histocompatibility complex, representing clusters of haplotypes that are preserved by selective pressure.

Sorting through the possibilities outlined in Smith et al.'s paper is certain to spur considerable future work, which promises to be most informative. The authors are to be commended for providing data that allow these several important issues to be raised, and by providing an interpretation that is both interesting and testable. Regardless of what subsequent findings reveal, they have performed a valuable experiment that will advance both skeletal genetics and skeletal physiology.

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