SYSTEMS ANALYSIS OF BONE FRAGILITY

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Advances in our understanding of the genetic basis of fragility fractures requires knowledge of how genes contribute to variation in physical traits that give rise to bone strength and toughness. Correlation metrics have been used to define higher-level functions for cardiovascular traits [1]. This approach uses Recombinant Inbred (RI) mouse strains to test multiple genetic perturbations that occur in a natural, non-pathological manner. The analytical method measures the tendency for traits to correlate after genetic randomization of the parental genomes in the RI panel. We tested whether this novel, network analysis could be used to study genetic variation in bone fragility.

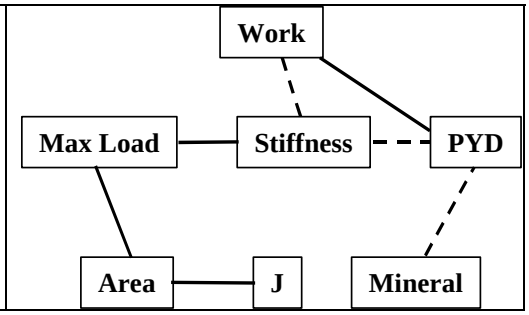
Femurs from 20 16-week old AXB/BXA RI mouse strains were phenotyped for mechanical properties, morphology, and mineral content. Using the mean values for each RI strain, a correlation matrix was established by relating each trait and property across the RI panel. Correlations exceeding a statistical threshold value of 0.66 were considered significant ($p<0.05$).

Genetic randomization was associated with significant variation in all traits and properties among the RI panel. The correlation matrix (Table 1) identified the traits and properties that cosegregate (i.e., remain functionally related) after randomization of AJ and B6 genes in the RI panel. To visualize these interactions, a hierarchical network (Fig 1) was constructed by linking the physical traits and mechanical properties that correlated significantly. This network correctly identified the functional interactions among the physical traits and the mechanical properties that were determined by independent means [2]. Thus, this network method is a powerful, multivariate approach for identifying physical traits that are deterministic of genetic variation in adult bone strength and fragility. Further, this approach can be extended to the next hierarchical level to identify the cellular processes that define adult bone size, shape, and quality. [1] Nadeau et al, 2003 Genome Res 13. [2] Jepsen et al, 2003 Mamm Genome 14.

Table 1. Correlation matrix. Significant correlations ($p<0.05$) are shown in gray. J=polar moment of inertia, PYD=post-yield deflection.

	Stiffness	Max Ld	PYD	Work	Area	J	Mineral
Stiffness	1.00	0.71	-0.72	-0.65	0.49	0.10	0.59
Max Ld		1.00	-0.57	-0.25	0.67	0.21	0.43
PYD			1.00	0.81	-0.19	0.20	-0.75
Work				1.00	-0.03	0.06	-0.61
Area					1.00	0.75	0.08
J						1.00	-0.29

Fig. 1. A network of functional interactions was constructed for bone based on analysis of RI mouse strains. The network was constructed hierarchically with physical traits arranged below mechanical properties. Solid and dashed lines indicate significant positive and negative correlations, respectively. Work-to-failure was moved outside the loop since it did not correlate significantly with any intrinsic bone trait.



Complex Trait Consortium, 2004
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