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NEWS AND COMMENTARY

Quantitative trait loci

Mapping the future of QTL's

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A recent paper published in Nature represents a first in the attempt to map and sequence a true quantitative trait loci (QTL) – a gene with a small effect and complex expression. This study highlights both the promise and hazards of the road ahead as we seek to diagnose all the genes contributing to complex phenotypes.

Diagnosing the genetic basis of quantitative traits – those characteristics that are controlled by many different genes and which exhibit relatively continuous phenotypic variation – has long been recognized as constituting a central challenge to researchers working on a wide variety of questions. Examples of quantitative traits range from agricultural yield to susceptibility to cancer, to a variety of evolutionary topics including growth rate, reproductive output, and even fitness (Falconer and Mackay, 1996). In this new study, Kroymann and Mitchell-Olds (2005) have mapped a QTL (a chromosomal segment containing one or more genes altering phenotype) affecting growth rate in *Arabidopsis thaliana* down to two loci. However, the remarkable observation is not which loci they found, but rather the manner in which the genes contribute to growth rate. The two loci each have a very small effect, are tightly linked within a 210-kb interval, and exhibit antagonistic epistatic interactions such that an allele at one locus could either increase or decrease growth rate depending on which allele is at the other locus. Indeed, had Kroymann and Mitchell-Olds not carefully controlled genetic background and explicitly considered epistasis, these loci would have been effectively invisible. To consider what this means for the genetic mapping of complex phenotypes, we need to consider some basic questions regarding the genetic basis of quantitative traits.

Efforts to analyze quantitative traits have focused on answering sets of related questions in two general areas. The first is 'the distribution of gene effects', which addresses the number of genes affecting a trait, their relative contribution, and physical location within the genome. The second is 'the mode of gene action', which focuses on establishing if a gene's effect on phenotype is constant (an additive effect), or contingent upon interaction with other genes (epistasis), the environment (GxE) or participation in multiple phenotypes (pleiotropy). Thus, we can categorize gene effect as additive *vs* nonadditive. These nonadditive gene effects are the hobgoblins of quantitative genetics, since they greatly complicate any attempt to dissect the genetic structure of complex traits. Yet they also have tremendous evolutionary implications, with the magnitude and prevalence of epistasis being one of the basic unanswered questions in evolutionary biology.

Thus, we can outline two extremes of genetic architecture (*distribution of effects + mode of gene action*) that determine a quantitative trait. In the first, a moderate number of genes each have a relatively large effect and all are strictly additive. In the second, a large number of genes contribute, each with a very small effect on phenotype, and each exhibits varying degrees of nonadditive interactions. The former would expedite our decomposition of quantitative traits into their component loci; the latter would complicate it.

These new data from Kroymann and Mitchell-Olds certainly suggest that the more complicated genetic architecture underlies quantitative traits. Indeed the authors' identification of this locus was entirely serendipitous, and the two loci would not be detectable in typical genome scan of loci affecting growth rate. This suggests that were one to carefully analyze many other such small intervals throughout the genome, then one would find many such small effect loci exhibiting complex nonadditive behavior contributing to the genetic basis of the trait we seek to describe.

There are then two important areas in which the study by Kroymann and Mitchell-Olds is significant. The first is how readily we will be able to determine the genetic basis of complex phenotypic traits, and the second is more specifically oriented toward the frequency and magnitude of epistasis. If the two loci they described typify all loci contributing to quantitative traits, then identifying all the loci contributing to phenotype and mapping them down to the level of the nucleotide will be a Herculean task.

However, it is worth noting that Kroymann and Mitchell-Olds did not extend their fine scale mapping experiment to other genomic intervals. Their findings at that pair of loci do not mean that other loci with a major effect on growth rate are not present elsewhere in the genome. And indeed there is no shortage of studies that identify QTL of large effect (Erickson *et al*, 2004). Yet, the results by Kroymann and Mitchell-Olds are not without precedent, and in the few cases where QTL intervals have been mapped down to the level of the gene, each QTL was observed to contain multiple genes, many of which exhibit significant nonadditive interactions (Mackay, 2004). As more studies move from QTL to gene, we will soon see if the complex genetic architecture suggested by Kroymann and Mitchell-Olds' study becomes the exception or the rule.

The observation of a significant and antagonistic epistasis between the two linked loci identified in this study contributes to a growing body of work that suggests that nonadditive gene effects are both prevalent and of a significant magnitude (Fenster *et al*, 1997; Peripato *et al*, 2004). This will clearly complicate the search for genes affecting phenotype. Indeed, epistasis is often referred to as 'cryptic variation.' The effect of an allele may depend on one or more other loci, such that an allele may have no effect on phenotype in one population and a significant effect in another due to differences in allele frequency (Templeton, 2000). However, epistasis and nonadditive gene effects should be regarded as something more than a nuisance in the dissection of complex traits. These phenomena reflect the cohesion of our genomes and can provide insight into the evolution of complex traits and even the mechanism of speciation (Li *et al*, 1997; Fenster and Galloway, 2000). The results by Kroymann and Mitchell-Olds highlight both the promise and the pitfalls of mapping quantitative traits down to the level of each contributing gene. It remains to be seen if the loci they describe are archetypal. But what is clear is that we have only begun to scratch the surface of determining how complex our complex phenotypes truly are.

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