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Seeing traits, close-up

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For the first time, researchers have discovered the molecular basis of a quantitative trait at the level of individual nucleotides. The report, appearing in the December issue of *Nature Genetics*, reveals that even the tiniest changes among a few genes can profoundly affect traits. The authors also describe an approach that can be used to characterize any trait in yeast -- and, potentially, higher organisms, they suggest.

In the current study, Adam Deutschbauer, now a postdoctoral fellow at the University of California, Berkeley, and Ronald Davis at Stanford University in California, focused on characterizing genes responsible for yeast sporulation efficiency, a measure of the rate at which spores emerge from their dormant state. Their approach revealed three genes responsible for the trait, two of which had never before been implicated in sporulation. Furthermore, single-nucleotide changes within genes or a regulatory region dramatically influenced the rate of yeast sporulation, suggesting that small changes can make a big difference to traits.

"This was the first time that multiple (nucleotides) have been identified for a single trait and the first time we've been able to reconstitute a quantitative trait just by changing single base pairs inside of a genome," Deutschbauer told *The Scientist*.

"I don't know of any other example where a complex trait was dissected to the resolution achieved in this study," said Lars Steinmetz, a geneticist at the European Molecular Biology Laboratory in Heidelberg, Germany.

Unlike single-gene mendelian traits, quantitative traits consist of multiple genes. Consequently, molecular characterization of these traits is fraught with problems from the outset, due to the complex interactions and the influence of multiple loci, genes, and environment.

To study sporulation efficiency, the authors crossed two well-characterized yeast strains: the high-efficiency SK1 strain and the low-efficiency S288c strain, and included all progeny for comparison. Using a series of genetic assays designed to hone in on regions of interest, they pinpointed three genes responsible for sporulation efficiency – *RME1*, *TAO*3, and *MKT*1.

No one had ever implicated *TAO3* or *MKT1* in sporulation, Deutschbauer noted, despite the fact that researchers had scrutinized that pathway. This observation underscores the power of quantitative trait analysis as a functional genomics tool, said Trudy Mackay, a geneticist at North Carolina State University in Raleigh, NC.

Next, the authors identified the individual nucleotides responsible for the difference in efficiency between the two parental strains, revealing a regulatory polymorphism in *RME1* and an amino acid polymorphism in both *TAO3* and *MKT1*. To confirm this, they substituted the nucleotides seemingly responsible for SK1's high-efficiency into the low efficiency S288c strain – and found that the engineered S288c strain sporulated with high-efficiency.

Their success stemmed from screening every strain and leaving no stone unturned -- anything less tells an incomplete story, according to scientists. "People thought, naively, that you could look at

sequences and see quantitative traits, but that's very biased," said Mackay. Similarly, "you can't just look for the candidate genes," explained computational biologist Paul Cliften, of Utah State University, Logan, UT. "You have to look at pretty much everything."

This exhaustive, unbiased approach "could be applied to any quantitative trait in yeast and could be applied to higher model organisms," Steinmetz told *The Scientist*. Just don't expect to see that happening anytime soon. "We've all wanted to do this [in higher organisms] but we can't put back a variant of an allele in the exact same place like you can in yeast," Mackay said.

Unlike the comparatively small genes present in yeast, higher organisms possess much larger genes, precluding the use of techniques constrained by gene size. "If it's this complicated for yeast," agreed Deustchbauer, "then it's going to be much, much more difficult for higher organisms."

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