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EPIGENETICS

An epigenetic twist on the missing heritability of complex traits


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Epigenetic variation has been suggested as an explanation for the missing heritability in complex traits. A study now reports that experimentally induced differentially methylated regions (DMRs) in *Arabidopsis thaliana* are stably inherited and act as epigenetic quantitative trait loci ($QTLs^{epi}$) independently of DNA sequence changes.

To contribute to complex-trait heritability independently of DNA sequence variation, at least some epigenetic stability during gametogenesis is necessary; that is, epigenetic states must be transmitted to the next generation intact. Cortijo and colleagues aimed to determine whether this stability is conferred by sequence-independent chromatin inheritance or by *cis*- or *trans*-acting DNA-based factors. The authors generated a population of epigenetic recombinant inbred *A. thaliana* lines (epiRILs) from two essentially isogenic parents that had highly divergent DNA methylomes. Previous work showed that the epiRILs segregate hundreds of stable parental DMRs throughout the genome. Using these DMRs as physical markers, the authors carried out classical linkage mapping in the epiRILs and identified various QTLs that underlie two highly heritable complex traits — primary root length and flowering time. The combined additive effects of these QTLs accounted for ~60% and ~90% of the heritability of primary root length and flowering time, respectively.

Linkage mapping results pinpointed the origin of the causal variants that underlie heritability to the parental generation as opposed to later inbred generations. The investigators then set out to eliminate the possibility that the causal variants underlying the QTLs were transposable element insertions in the parental line that shows reduced DNA methylation by re-sequencing a large number of epiRILs. Although four shared transposable element insertions were found in several QTLs of the two traits, further work showed that they were not causal. The epiRIL QTLs are therefore most likely the result of the heritable, induced loss of DNA methylation in the QTL intervals.

About 30% of the induced heritable DMRs that were identified in the epiRILs overlap with naturally occurring DMRs. The authors propose that these DMRs could also act as $QTLs^{epi}$ in natural populations and thus constitute a measurable component of the missing heritability of complex traits.

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ORIGINAL RESEARCH PAPER Cortijo, S. *et al.* Mapping the epigenetic basis of complex traits. *Science* http://dx.doi.org/10.1126/science.1248127 (2014)

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