COMPLEX TRAITS

Missing in action

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Explanations for ‘missing heritability’ — the shortfall in the proportion of heritable phenotypic variation for a trait that can be explained by identified loci — are hotly debated, particularly in human disease genetics. A study has now examined the sources of missing heritability in yeast and provides evidence about genetic architecture, such as the role of genetic interactions, which could influence future study designs.

Bloom *et al.* studied a panel of >1,000 haploid segregants from a cross between a laboratory strain and a wine strain of *Saccharomyces cerevisiae*. Each segregant was genotyped in detail using short-read sequencing and was subjected to a large panel of different conditions, such as different carbon sources, small molecules or temperatures.

Using high-throughput assays, the authors obtained measurements for the growth of each segregant under each condition, thus giving them a readout for 46 quantitative traits.

For each trait, the phenotypic variation among segregants is dependent on the ‘broad-sense’ heritability (that is, the contribution of heritable genetic factors) and on random environmental effects. The observed variation can also be influenced by measurement errors. As the environmental conditions were tightly controlled and measurements were repeated, the authors were able to estimate broad-sense heritabilities. There can be multiple contributors to broad-sense heritability: genetic factors that work additively (known as ‘narrow-sense’ heritability), gene–gene interactions, gene–environment interactions and dominance effects. Because this study used haploid yeast in uniform environments, the authors were able to work on the basis that the broad-sense heritability they observed resulted only from additive factors and gene–gene interactions.

The next step was to work out the relative contribution of these two factors. To estimate narrow-sense heritability, the authors used an approach in which phenotypic similarity among individuals is compared with their genetic relatedness. For each trait, they could then estimate the contribution of gene–gene interactions by subtracting the narrow-sense heritability estimate from the broad-sense estimate; the range of the predicted contribution of interactions was from ~0% to ~54%.

So what proportion of heritability can be pinned down to specific loci?

Using quantitative trait locus (QTL) mapping approaches, Bloom *et al.* detected between 5 and 29 significant QTLs per trait, and most QTLs had small effects. The identified loci explained 72–100% of the estimated narrow-sense heritability, and the authors provide evidence that insufficient sample size is the reason for the remaining ‘missing’ loci.

The authors then looked for significant pairwise QTL–QTL interactions and found interactions for 24 of the traits. However, the detected interactions generally explained only a small part of the difference between broad-sense and narrow-sense heritability. Reasons for this might include the lower power of the study to detect interactions compared with additive effects, small effect sizes of interactions or the presence of higher-order interactions.

Clearly, the loci identified in this study explain a far higher proportion of trait heritability than has been achieved in human genome-wide association studies. There are numerous possible reasons for this difference, including dominance effects in diploid organisms and the potentially greater inherent complexity of many human traits. However, this work is consistent with idea that many loci with small effect are important in narrow-sense heritability, thus supporting the strategy of increasing sample sizes to detect more loci.

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ORIGINAL RESEARCH PAPER Bloom, J. S. *et al.* Finding the sources of missing heritability in a yeast cross. *Nature* 3 Feb 2013 (doi:10.1038/nature11867)

FURTHER READING Tenesa, A. & Haley, C. S. The heritability of human disease: estimation, uses and abuses. *Nature Rev. Genet.* **14**, 139–149 (2013)