COMPLEX DISEASE

Rare treasures

Rare variants distributed across large genomic regions make a substantial contribution to the genetic basis of complex diseases, according to a simulated genome-wide association (GWA) study that is backed by real disease-mapping data.

GWA studies are based on the assumption that complex diseases are caused by many common variants of small effect, and the signals observed in GWA studies are assumed to correspond to common variants. The hypothesis tested by Goldstein and colleagues is whether, in fact, GWA signals might be due to one or more rare variants that end up having a portion of their effects 'credited' to common variants (a possibility that the authors call 'synthetic associations').

The simulated case–control studies involved 2,000–6,000 subjects who carried a realistic number of rare alleles of varying effect size. The virtual GWA study produced some interesting results. A third of the simulations picked up synthetic associations between at least one rare variant and a common allele. In addition, associations were identified even if the causal variants were located several megabases from the SNP — farther than previously thought — or even when the SNP and the variant were separated by recombination. Synthetic association can therefore be very strong; however, this also means that sequencing around the SNP for causal variants could be fruitless.

The model is supported by work from co-author Hakonarson that demonstrates strong synthetic associations for two medical conditions at the extremes of the Mendelian–complex disease spectrum. This perspective suggests that the genomic distribution of GWA signals for traits of interest might help in interpreting whole-genome sequence data for those traits.

Tanita Casci

ORIGINAL RESEARCH PAPER Dickson, S. P., Wang, K., Krantz, I., Hakonarson, H. & Goldstein, D. B. Rare variants create synthetic genome-wide associations. *PLoS Biol.* **8**, e1000294 (2010)