Quantitative Biology > Populations and Evolution

Narrowing the gap on heritability of common disease by direct estimation in case-control GWAS

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One of the major developments in recent years in the search for missing heritability of human phenotypes is the adoption of linear mixed-effects models (LMMs) to estimate heritability due to genetic variants which are not significantly associated with the phenotype. A variant of the LMM approach has been adapted to case-control studies and applied to many major diseases by Lee et al. (2011), successfully accounting for a considerable portion of the missing heritability. For example, for Crohn's disease their estimated heritability was 22% compared to 50-60% from family studies. In this letter we propose to estimate heritability of disease directly by regression of phenotype similarities on genotype correlations, corrected to account for ascertainment. We refer to this method as genetic correlation regression (GCR). Using GCR we estimate the heritability of Crohn's disease at 34% using the same data. We demonstrate through extensive simulation that our method yields unbiased heritability estimates, which are consistently higher than LMM estimates. Moreover, we develop a heuristic correction to LMM estimates, which can be applied to published LMM results. Applying our heuristic correction increases the estimated heritability of multiple sclerosis from 30% to 52.6%.

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