

A gene-based approach to epistasis.

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Abstract:

This presentation describes a methodology for detecting gene-gene interaction (epistasis) in the context of large-scale genetic association studies. Although epistasis is often talked about, both as a ubiquitous biological reality and as a potential reason for failure to replicate main-effects association studies, the study of epistasis in complex human phenotypes is typically relegated only to secondary, exploratory and under-powered analysis. In this talk, I suggest that utilizing a multivariate statistical technique to perform a gene-based analysis, simultaneously considering all markers in two genes or regions, can substantially increase power and reduce the number of tests that must be performed. This approach works particularly well when paired with the efficient case-only design for detecting interaction, although one crucial assumption of the case-only design is that the two loci are independent in the general population: consequently, ensuring that the case sample is genetically homogeneous becomes vital. To fully realize the potential of the case-only design, it will be particularly important to apply genetic background methods to detect potential population stratification (in the context of the kind of large-scale association studies that are imminent, thousands of markers will routinely be available for this purpose).

Ultimately, the goal is to provide a powerful, efficient and robust gene-based screening tool for epistasis in large case-only or case-control samples, that can handle thousands of genetic markers across hundreds or even thousands of genes.