

Power to find linkage in epistatic models: Comparison between the symmetric two- and three-stage and the Guo-Elston procedures

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Abstract:

The strategies used to identify the gene causing a Mendelian disease have had limited success when they are applied in the search for genes responsible for complex disorders. The low power observed with these methods is attributable to the fact that linkage signals in complex diseases are typically weak.

During the 1950's, Cochran, Finney, and Curnow developed varietal selection methods that selected the most promising variety of a crop in a limited number of stages. They concluded that the optimum design should be symmetric in the sense that the same amount of resources is used at each stage.

We apply this procedure to the genetics problem of identifying disease genes causing a complex disorder. A similar approach already exists in the literature; the search procedures developed by Elston, Guo, Williams in 1996, and Guo, and Elston in 2000 work in stages. We compare these two methodologies using three epistatic models studied by Rice and Neuman.

Using the mean statistic for affected sib-pairs and the proportion of sib-pairs sharing zero alleles IBD and defining the power of search procedure as the probability to find both disease alleles, we found that:

- In general, the mean statistic for affected sib-pair has more power than the proportion of sib-pairs sharing zero allele IBD and is more cost effective.
- In almost all simulations, the symmetric two-stage procedure is: more powerful, more robust to phenocopy and more cost effective than the both the Elston, Guo and Williams and the Guo-Elston procedures.