

Generalized MDR Approaches to Detecting Multifactor Interactions in Population-based and Family-based Studies

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Abstract

Widespread but elusive multifactor (i.e., gene-gene, $G \times G$, and gene-environment, $G \times E$) interactions present a significant challenge in determining risk factors of complex diseases. The traditional methods are typically underpowered because of the problem referred to as the “curse of dimensionality.” Several combinatorial approaches, such as the multifactor dimensionality reduction (MDR) method, the combinatorial partitioning method (CPM), and the restricted partition method (RPM), have emerged as a promising tool for better detecting $G \times G$ and $G \times E$ interactions. To overcome the limitations in the existing combinatorial approaches, such as not allowing justification for covariates, which may reduce the prediction ability and statistical power, we develop a generalized MDR (GMDR) statistical framework by using a class of more efficient and comprehensive statistics (e.g., the score statistic) that permits adjustment for discrete and quantitative covariates and is applicable to both dichotomous and continuous phenotypes in various population-based study designs. Further, a pedigree-based GMDR (PGMDR) is extended for handling arbitrary pedigree structures, arbitrary patterns of missing marker genotypes in founders, and arbitrary phenotypes. Computer simulations provide evidence that the proposed methods are superior in performance to identify epistatic loci compared to the existing combinatorial methods. Lastly, we apply the proposed approach to a genetic dataset on tobacco dependence and find a significant epistatic interaction in affecting nicotine dependence.