

The MDR-PDT for Identifying Joint Genetic Effects for Complex Diseases in Families

Eden R. Martin PhD

Associate Research Professor

Duke University, Section of Medical Genetics

Abstract:

Complex genetic diseases are marked by the presence of many factors contributing independently to risk or through interaction. It is now well recognized that gene-gene and gene-environment interactions are important in complex diseases, and statistical methods to detect interactions are becoming more widespread. Traditional parametric approaches are often limited in their ability to detect high-order interactions and generally handle sparse data, and standard stepwise procedures may miss interactions that occur in the absence of detectable main effects. To address these limitations, the multifactor dimensionality reduction (MDR) method (Ritchie et al. 2001) was developed. The MDR is particularly well-suited for examining high-order interactions and detecting interactions even in the absence of main effects. The MDR was originally designed to test balanced case-control data. The test can use family data, but requires a single matched pair be selected from each family. This may be a discordant sib pair, or may be constructed from triad data when parents are available. To take advantage of additional affected and unaffected siblings requires a test statistic that measures the association of genotype with disease in general nuclear families. We have developed a novel test, the MDR-PDT, by merging the MDR method with the genotype-Pedigree Disequilibrium Test (geno-PDT; Martin et al. 2003). MDR-PDT will allow us to identify single-locus effects or joint effects (independent or gene-gene interactions) of multiple loci in families of diverse structure. We have used simulations to demonstrate the validity of the test and examine its power. To examine its applicability to real data, we applied the MDR-PDT to data from candidate genes for Alzheimer disease (AD) in a large family dataset.