

Case-Only and Other Design Strategies for Tests of Gene x Environment Interaction

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Abstract:

Assessment of gene-gene (GxG) or gene-environment (GxE) interaction has become an important avenue of research. Case-based designs such as the case-only and case-parent trio designs have been advocated for interaction studies as an alternative to the traditional case-control or nested case-control approach. Under the assumption of independence between the putative interacting factors in the general population, any association between these factors among cases can be taken as evidence for interaction with respect to disease risk. The case-only design, and several designs using complete risk factor information on cases but only partial information on controls (partial case-control designs), have been suggested to be more efficient than case-control designs for tests of interaction¹. However, it is still unclear how often this independence assumption is violated, how detrimental such violations actually are, or which kinds of designs and test statistics for interaction are most robust to such departures. We have explored the use of case-only, partial case-control and caseparent trio designs across a wide range of different GxE interaction models, especially in situations where a dependency exists between the G and E factors in the population, either due to a true relationship between the G and E factors, or due to correlation induced by bias such as population substructure. We compare the utility of these designs across several simulation scenarios and also evaluate the extent to which such GxE dependence actually exists in 4 observed nested case-control data sets collected by our collaborators at Johns Hopkins.