

Epigenome-wide Analyses of Sparse Mediation Effects Under Composite Null Hypotheses

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Abstract

An epigenome-wide mediation analysis is conducted to investigate whether epigenetic variations M mediate the effect of socioeconomic adversity S on adiposity Y . The mediation effect can be expressed as a product of two parameters: the S - M association and the M - Y association conditional on S . We show that the joint significance test examining the two parameters separately has smaller p -values than the normality-based or the normal product-based test for the product and is a size α test. However, under multiple tests, the joint significance test has a conservative test size and low power within the epigenomic study because it fails to account for the composition of different null hypotheses. We develop a new test assessing the product of two normally distributed test statistics under a composite null hypothesis, where either one parameter is zero or both are zero. We show that the null composition can be adjusted by variances of test statistics without directly estimating proportions of different nulls. Advantages of the new test are illustrated in simulation and the epigenomic study. The new test identifies two methylation loci of the *FASN* gene mediating the socioeconomic effect on adiposity with the false discovery rate less than 10% while existing methods had none surviving this cut-off.