

Rank Tests for Trend in Genetic Association Studies with Quantitative Traits

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Abstract: Testing against order-restricted alternatives in a k-sample location problem arises frequently in the sciences, biomedical applications, and more recently in genetics. Nonparametric tests for trend, such as the Jonckheere test, have higher power than normal theory tests when the underlying distribution is non-normal. These tests are well-known to statisticians however have not been widely used in genetic practice. We apply Jonckheere's test and its modification (first introduced by Tryon and Hettmansperger, 1973) to the problem of detecting association between genetic markers and quantitative phenotypes. Our simulations show that the test maintains its size and is asymptotically normal even in the presence of extreme disparities in sample sizes.

These rank tests are optimal for detecting linear trends, expected under the assumption of a co-dominant genetic model. For dominant or recessive models however, (i.e., when the alternative is on the boundary of the parameter space) other tests may be more powerful than Jonckheere's. Since the underlying genetic model is often unknown, we explore robust procedures, including a linear combination (MERT) and a maximum (MAX) of the optimum statistics for linear, convex and concave alternative shapes. While these more computationally involved procedures offer better protection against model misspecification, we show that because of the imbalance in sample sizes and the unequal probability of different models, the simpler Jonckheere or weighted Jonckheere tests may perform just as well in practice as their robust counterparts.