Statistical validity and power for testing for heterogeneous effects with quantitative traits in pharmacogenetic studies

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In pharmacogenetic studies, it is often of interest to look for evidence of a difference in treatment effect in complementary groups. Such groups are typically defined based on a 1) single nucleotide polymorphism (SNP) (for example allele A is dominant: AA, Aa versus aa), 2) traditional classification of metabolizing group (e.g. poor versus extensive metabolizes), or categorized by number of active (fully functional) alleles (e.g. at least one versus none). When the trait is quantitative and the comparison is between two groups, the conventional t-test or rank sum test are often used. To detect differences when heterogeneity is present, O'Brien proposed extensions to the t-test and rank sum test and called these tests generalized t-test and generalized rank sum test. The generalized tests involve using either ordinary least squares or logistic regression where group membership is regressed against the trait using a quadratic model. We extend the generalized tests by using restrictive cubic splines. The statistical properties under different allele frequencies, type of gene action, effect size, distributions (normal, log normal, and contaminated normal) were evaluated. Additionally, alternative hypothesis were generated assuming only a location shift, only a scale shift, and both location and scale shift. The generalized test using splines and O'Brien's generalized tests are compared with the t-test, rank sum, and the Siegel-Tukey test. The generalized t-test using splines performed well in regard to power when the distributions are skewed or contaminated. The method provided no improvement over the generalized t-test when there was only a shift in location. The properties will be discussed with regard to the general usage of tests for detecting heterogeneity and illustrated using data from a pharmacogenetic study.