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Combining Linear and Quadratic Tests for Rare Variants Provides a Robust Test Across Genetic Models

Rare variants play an important role in complex human diseases and traits. Although many association tests have been proposed for rare variants, there is much confusion about the practical choice of a good test. Recent evaluations categorize methods into two classes: linear statistics sensitive to specific directional alternatives or the omnibus quadratic statistics. However, neither type of tests consistently outperforms the other. To achieve robustness, we consider the minimal p-value approach and the Fisher's method of combining p-values from linear and quadratic tests. Analytical and extensive simulation studies show that both methods are robust across genetic models with varying parameters.