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rMATS: Robust and Flexible Detection of Differential Alternative Splicing from Replicate RNA-Seq Data

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Ultra-deep RNA sequencing has become a powerful approach for genome-wide analysis of pre-mRNA alternative splicing. We previously developed MATS, a statistical method for detecting differential alternative splicing between two RNA-Seq samples. We describe a new statistical model and computer program, rMATS (replicate MATS), designed for detection of differential alternative splicing from replicate RNA-Seq data. rMATS uses a hierarchical model to simultaneously account for sampling uncertainty in individual replicates and variability among replicates. rMATS outperformed two existing methods for replicate RNA-Seq data in all simulation settings, and RT-PCR yielded a high validation rate (94%) in an RNA-Seq dataset of prostate cancer cell lines. Our data also provide guiding principles for designing RNA-Seq studies of alternative splicing. We demonstrate that it is essential to incorporate biological replicates in the study design. Of note, pooling RNAs or merging RNA-Seq data from multiple replicates is not an effective approach to account for variability, and the result is particularly sensitive to outliers. As the popularity of RNA-Seq continues to grow, we expect rMATS will be useful for studies of alternative splicing in diverse RNA-Seq projects.

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