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RASA: Robust Alternative Splicing Analysis for Human Transcrip-tome Arrays

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Abstract

Motivation

Many human diseases are known to involve abnormal alternatively spliced RNA transcripts which can serve as diagnostic biomarkers and candidate targets for therapy. Human transcriptome arrays (HTA) have recently been developed for high throughput transcriptome profiling in biomedical studies by measuring alternative splicing signals not only from exons but also from exon-exon junctions. Effective use of these rich signals requires the development of computational methods for better gene and alternative splicing analyses.

Results

In this work, we introduce a computational method, Robust Alternative Splicing Analysis (RASA), for the analysis of the new transcriptome arrays by effective integration of the exon and junction signals. To increase the robustness of gene expression estimation, the algorithm first calculates the expression index of each gene by selecting exons classified as not alternatively spliced between the groups of samples. It then identifies alternatively spliced exons that are supported by both exon and junction signals to reduce the false positives. Finally, it detects additional alternative splicing candidates that are supported by only exon signals because the signals from the corresponding junctions are not well detected. The performance of the RASA was tested using data of human liver and muscle samples on Affymetrix HTAs, and evaluated with results of RNA-Seq analyses. The validation rate is 52.4%, which is a 60% increase when comparing with previous methods that do not use selected exons for gene expression calculation and junction signals for splicing detection. Additionally, nine candidates were chosen to be further tested with RT-PCR and were validated. Another analysis with a custom-designed HTA platform also showed similar performance. These results suggest that the RASA algorithm significantly improves alternative splicing analyses on HTA platforms.

Availability**:** http://igenomed.stanford.edu/~junhee/RASA/top.html