Docket #: S16-250

MACHETE – algorithm for automated detection of RNA gene fusions

Researchers in Prof. Julia Salzman's laboratory have developed a sensitive, specific algorithm for automated, high-throughput detection of RNA fusions from RNA-Seq data. This technology, called MACHETE (Mismatched Alignment ChimEra Tracking Engine), uses statistical analysis to detect fusion events including splicing between exons separated by more than 100kb or splicing of genes on different chromosomes. It creates a custom database of all exon-exon junctions and prioritizes fusion transcripts for further study by weeding out false positives while retaining true positives. This approach removes false positives from biochemical and bioinformatics artifacts, resulting in unprecedented specificity (no false positives when run on gold standard simulated data) with sensitivity comparable to the best performing published algorithms. Furthermore, the algorithm can analyze short reads and does not require human-guidance for filtering results. MACHETE could potentially pave the way for unbiased de novo discovery of potentially driving and druggable gene fusions in primary tumors with applications in research, diagnostics and drug development.

Stage of Research
The inventors have benchmarked MACHETE's sensitivity and specificity against the best performing published algorithms. In addition, they have used MACHETE to mine public data to discover and validate novel gene fusions in ovarian cancer.

Applications

- **Biomarker discovery** - identify novel gene fusions, particularly tumor-specific fusions associated with cancer
- **Diagnostic sequencing** - identify fusion genes associated with a patient's disease for treatment planning or monitoring disease progression
- **Target discovery** - identify druggable gene fusions in primary tumors

Advantages

- **High specificity** - MACHETE had no false positives when run on simulated reference human transcriptome data, achieving an essentially null background on cytogentically normal samples
- **Sensitive de novo detection** - performs as well as current algorithms in detecting gene fusions in multiple gold standard cell lines and has identified fusions missed by other algorithms
- **Automated for high throughput analysis:**
    - unsupervised detection does not require human-guided manual filtering of results
    - transparent and makes no ad hoc or heuristic choices

Publications

- R. Dehghannasiri, D.E. Freeman, M. Jordanski, G. L. Hsieh, A. Damljanovic, E. Lehnert and J. Salzman Improved detection of gene fusions by applying statistical methods reveals oncogenic RNA cancer drivers *PNAS* July 30, 2019.
- Gillian Hsieh, Rob Bierman, Linda Szabo, Alex Gia Lee, Donald E. Freeman, Nathaniel Watson, E. Alejandro Sweet-Cordero and Julia Salzman Statistical algorithms improve accuracy of gene fusion detection *Nucleic Acids Research* (2017).

Patents

- Published Application: WO2018152542
- Published Application: 20200202980
- Issued: 11,615,864 (USA)

Innovators

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