Indel detection from DNA and RNA sequencing of primary and advanced prostate cancer

Rendong Yang[1,2], Jamie L. Van Etten[3], Scott M. Dehm[2,3]

[1] The Hormel Institute, University of Minnesota, Austin, MN 55912.

[2] Masonic Cancer Center, University of Minnesota, Minneapolis, MN 55905.

[3] Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55905

Background: Insertions and deletions (indels) are a major class of genomic variation associated with human disease. Indels are primarily detected from DNA sequencing (DNA-seq) data but their transcriptional consequences remain unexplored due to challenges in discriminating medium-sized and large indels from splicing events in RNA-seq data.

Methods: We developed transIndel, a splice-aware algorithm that parses the chimeric alignments predicted by a short read aligner and reconstructs the mid-sized insertions and large deletions based on the linear alignments of split reads from DNA-seq or RNA-seq data. TransIndel exhibits competitive or superior performance over eight state-of-the-art indel detection tools on benchmarks using both synthetic and real DNA-seq data.

Results: We applied transIndel to DNA-seq and RNA-seq datasets from 333 primary prostate cancer patients from The Cancer Genome Atlas (TCGA) and 59 metastatic prostate cancer patients from AACR-PCF Stand-Up- To-Cancer (SU2C) studies. TransIndel enhanced the taxonomy of DNA- and RNA-level alterations in prostate cancer by identifying recurrent FOXA1 indels as well as exitron splicing in genes implicated in disease progression.

Conclusions: Our study demonstrates that transIndel is a robust tool for elucidation of medium- and large-sized indels from DNA-seq and RNA-seq data. Including RNA-seq in indel discovery efforts leads to significant improvements in sensitivity for identification of med-sized and large indels missed by DNA-seq, and reveals non-canonical RNA-splicing events in genes associated with disease pathology.

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