Genotyping structural variation in variation graphs with the vg toolkit

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Abstract

Introduction

Structural variation (SV) represents genomic mutation involving 50 bp or more and can take several forms, such as for example deletions, insertions, inversions, or translocations. Although whole-genome sequencing (WGS) made it possible to assess virtually any type of structural variation, many challenges remain. In particular, SV-supporting reads are difficult to map to reference genomes. Multi-mapping, caused by widespread repeated sequences in the genome, is another issue because it often resembles SV-supporting signal. As a result, many SV detection algorithms have been developed and multiple methods must usually be combined to minimize false positives. Several large-scale projects used this ensemble approach, cataloging tens of thousands of SV in humans[1,2]. SV detection from short-read sequencing remains laborious and of lower accuracy, explaining why these variants and their impact have been under-studied as compared to single-nucleotide variants (SNVs) and small insertions/deletions (indels).

Over the last few years, exciting developments in sequencing technologies and library preparation made it possible to produce long reads or retrieve long-range information over kilobases of sequence. These approaches are maturing to the point were it is feasible to analyze the human genome. This multi-kbp information is particularly useful for SV detection and de novo assembly. In the last few years, several studies using long-read or linked-read sequencing have produced large catalogs of structural variation, the majority of which were novel and sequence-resolved[3,4,5,6] (*REF_PETER_SOON*). These technologies are also enabling high-quality de novo genome assemblies to be produced[3,7], as well as large blocks of haplotype-resolved sequences[8]. These technological advances promise to expand the amount of known genomic variation in humans in the near future.

In parallel, the reference genome is evolving from a linear reference to a graph-based reference that contains known genomic variation[10,11,9]. By having variants in the graph, mapping rates are increased and variants are more uniformly covered, including indels and variants in complex regions[10]. Both the mapping and variant calling become variant-aware and benefit in term of accuracy and sensitivity. In addition, different variant types are called simultaneously by a unified framework. Graphs have also been used locally, i.e. to call variants at the region level. GraphTyper[12] and BayesTyper[13] both construct variation graphs of small regions and use them for variant genotyping. Here again, the graph-approach showed clear advantages over standard approaches that use the linear reference. Other SV genotyping approaches compare read mapping in the reference genome and a sequence modified with the SV. For example SMRT-SV was designed to genotype SVs identified on PacBio reads[4], SVTyper uses paired-end mapping and split-read mapping information[14], and Delly provides a genotyping feature in addition to its discovery mode[15].

Results

Methods

Discussion

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