Comprehensive detection of germline and somatic structural mutation in cancer genomes by Bionano Genomics Optical Mapping

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Abstract

The ability to identify structural variants (SVs) is crucial in cancer genetics. Karyotype and cytogenetics are manually intensive. Microarrays and sequencing cannot detect calls in segmental duplications and repeats, miss balanced variants and low-frequency mutations.

We describe Bionano’s Saphyr platform to identify SVs in cancer genomes. DNA >100 kbp is extracted, labeled at specific motifs, and linearized through NanoChannel arrays. Molecule images are digitized and de novo assembled, creating chromosomal arm scale genome maps. Cancer mutations >500 bp are detected by aligning the molecules or the genome maps to the public reference.

We ran Bionano’s cancer workflow on multiple human cancer cell lines. While the number of SVs varies among samples, we typically observe >3,500 calls per genome. In the SK-BR-3 breast cancer genome, we detected a cluster of amplifications, and translocations on chr8, impacting the gene MYC. In the CML genome K562, the BCR-ABL translocation was detected, while we also detected novel rearrangements, such as insertion and inversion disrupting the gene NAAALD2 in a prostate cancer cell line LNCaP.

In conclusion, with one platform, Saphyr can discover a broad range of traditionally refractory but relevant SVs, and improves our understanding of cancer.

Background

Generating high-quality finished genomes replete with accurate identification of structural variation and high completion (minimal gaps) remains challenging using short read sequencing technologies alone. The Saphyr™ system provides direct visualization of long DNA molecules in single steps, bypassing the statistical inference needed to align paired-end reads with an uncertain insert size distribution. These long labeled molecules are de novo assembled into physical maps spanning the entire diploid genome. The resulting provides the ability to correctly position and orient sequence contigs into chromosome-scale scaffolds and detect a large range of homozygous and heterozygous structural variation with very high efficiency.

Methods

(1) Long molecules of DNA are labeled with Bionano reagents by (2) incorporation of fluorophores at a specific sequence motif throughout the genome. (3) The labeled genomic DNA is then linearized in the Saphyr Chip using NanoChannel arrays (4) Single molecules are imaged by Saphyr and then digitized. (5) Molecules are uniquely identifiable by distinct distribution of sequence motif labels (6) and then assembled by pairwise alignment into de novo genome maps.

Conclusions

We demonstrate that the Saphyr system can be used to accurately detect genetic mutation hallmarks in samples with cancer. These include large rearrangements ranging from translocations, within chromosome fusions, to copy number alterations. Researchers can perform experiments to uncover somatic variation by comparing with Bionano control sample database, or against a matched pair sample. Furthermore, Bionano SV pipelines can detect SVs with complex breakpoint structures that are recall-critical to detection by other technologies. Our results indicate that the Saphyr system can capture a broad spectrum of variation with functional importance, and can provide easy solutions for cancer studies.

References