Comprehensive Detection of Germline and Somatic Structural Mutation in Cancer Genomes by Bionano Genomics Optical Mapping

A.W.C. Pang1, J. Lee1, K. Hong1, T. Anantharaman1, E.T. Lam1, Y. Delpu1, S. Bocklandt4, S. Marin1, A. Hastie1, M. Borodkin1

1Bionano Genomics, San Diego, California, United States of America

Abstract

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

Materials and Methods: We describe the Bionano Genomics’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.

Results: Over the past 12 months, the power of Bionano’s cancer workflow has been demonstrated on nearly 50 various cancers, including leukemia, breast, ovarian, prostate, pancreatic, among others. While the number of SVs varies among samples, we typically observe ~3500 calls per genome. Among leukemia samples, we captured the BCR-ABL1 translocation as well as deletions impacting tumor suppressor genes such as PTEN14 and ESRRG. We resolved the structure of large duplications (790 kbp) disrupting BRCA1 in early-onset breast cancers, found the amplification of MYC in lung cancers. Conclusions: In conclusion, with one platform, Saphyr can discover a broad range of traditionally refractory but relevant SVs, and improves our understanding of cancer.

Methods

1. Extraction of long DNA molecules
2. Label DNA at specific sequence motifs
3. Saphyr Chip linearizes DNA in NanoChannel arrays
4. Saphyr automates imaging of single molecules in NanoChannel arrays
5. Molecules and labels detected in images
6. Bionano Access software assembles optical 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 recalcitrant 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.

Reference
