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Structural variant analysis of a cancer reference cell line sample using multiple sequencing technologies

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Abstract

Background: The cancer genome is commonly altered with thousands of structural rearrangements including insertions, deletions, translocation, inversions, duplications, and copy number variations. Thus, structural variant (SV) characterization plays a paramount role in cancer target identification, oncology diagnostics, and personalized medicine. As part of the SEQC2 Consortium effort, the present study established and evaluated a consensus SV call set using a breast cancer reference cell line and matched normal control derived from the same donor, which were used in our companion benchmarking studies as reference samples.

Results: We systematically investigated somatic SVs in the reference cancer cell line by comparing to a matched normal cell line using multiple NGS platforms including Illumina short-read, 10X Genomics linked reads, PacBio long reads, Oxford Nanopore long reads, and high-throughput chromosome conformation capture (Hi-C). We established a consensus SV call set of a total of 1788 SVs including 717 deletions, 230 duplications, 551 insertions, 133 inversions, 146 translocations, and 11 breakends for the reference cancer cell line. To independently evaluate and cross-validate the accuracy of our consensus SV call set, we used orthogonal methods including PCR-based validation, Affymetrix arrays, Bionano optical mapping, and identification of fusion genes detected from RNA-seq. We evaluated the strengths and weaknesses of each NGS technology for SV determination, and our findings provide an actionable guide to improve cancer genome SV detection sensitivity and accuracy.



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Table of Contents The Cancer Reference

1. Understanding the eBook The Cancer Reference
 - The Rise of Digital Reading The Cancer Reference
 - Advantages of eBooks Over Traditional Books
2. Identifying The Cancer Reference
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an The Cancer Reference
 - User-Friendly Interface
4. Exploring eBook Recommendations from The Cancer Reference
 - Personalized Recommendations
 - The Cancer Reference User Reviews and Ratings
 - The Cancer Reference and Bestseller Lists
5. Accessing The Cancer Reference Free and Paid eBooks
 - The Cancer Reference Public Domain eBooks
 - The Cancer Reference eBook Subscription Services

- The Cancer Reference Budget-Friendly Options
- 6. Navigating The Cancer Reference eBook Formats
 - ePub, PDF, MOBI, and More
 - The Cancer Reference Compatibility with Devices
 - The Cancer Reference Enhanced eBook Features
- 7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of The Cancer Reference
 - Highlighting and Note-Taking The Cancer Reference
 - Interactive Elements The Cancer Reference
- 8. Staying Engaged with The Cancer Reference
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers The Cancer Reference
- 9. Balancing eBooks and Physical Books The Cancer Reference
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection The Cancer Reference
- 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
- 11. Cultivating a Reading Routine The Cancer Reference
 - Setting Reading Goals The Cancer Reference
 - Carving Out Dedicated Reading Time
- 12. Sourcing Reliable Information of The Cancer Reference
 - Fact-Checking eBook Content of The Cancer Reference
 - Distinguishing Credible Sources
- 13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development
 - Exploring Educational eBooks
- 14. Embracing eBook Trends

- Integration of Multimedia Elements
- Interactive and Gamified eBooks

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