Detecting a Novel Range of Large Somatic Genomic Rearrangements in Human Cancer Using the Bionano Optical Mapper

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ABSTRACT
Whole genome sequencing has revealed complex genomic rearrangements to be common molecular events driving human cancer, in particular prostate carcinogenesis. Detecting the full range and subtypes of large structural variants (SVs), greater than one kilobase (kb) in length, is however challenging when using clinically feasible short-read next generation sequencing (NGS) technologies alone.

In this study we combine short-read single base resolution NGS with megabase resolution next generation mapping (NGM) using the Bionano optical mapper, to test for feasibility and necessity for the inclusion of NGM in the future practice of precision medicine for prostate cancer.

Applying NGM to both primary and metastatic prostate cancer we uncover a novel spectrum of large genomic rearrangements undetectable using short-read NGS alone.

Based on our findings, we hypothesise that large genomic rearrangements undetectable using short-read NGS alone.

INTRODUCTION
Next Generation Mapping (NGM)

RESULTS: Primary Prostate Cancer

Almost 90% of NGM-called SVs were novel, involving a potential novel fusion gene (Fig.4), with a predominance of insertion / duplication events over deletions (12/15) directly impacting a gene of known oncogenic potential (example Fig.5), while 54% of NGM-SVs were validated via manual inspection of NGS data.

FIGURE 5. NGM-derived 4 Kb somatic insertion within the tumor suppressor gene CNTF (chromosome 3: 284,661-305,427) identified in patient UP2153. While the tumor map (blue track) showed a 2.5 kb insertion (Chr3: 302.9 - 305.4 Kb) relative to Hg19 (aqua track), defined by a tandem repeat interval (inset), direct comparison of the tumor to matched blood genome maps (red track) found a larger 4 Kb insertion.

ACKNOWLEDGMENTS

FIGURE 7. Novel potential prostate cancer metastatic oncogenic driver. A NGM-derived 15.6 Kb somatic deletion within CDH10, known to code for cadherin and involved in cell junction organization and ERK signaling. Mutations within CDH10 have previously been reported in colorectal cancer and lung squamous cell carcinoma, but this may be the first implication for prostate cancer.

BLOOD NGM
TUMOR NGM

DECEASED

Each patient carried two unique somatic potentially novel actionable or driver oncogenic large SVs not detected using NGS (Examples in Fig.6, Fig.7 and Fig.8).

FIGURE 6. Novel potential prostate cancer metastatic oncogenic driver. A NGM-derived 68kbp somatic deletion within CDH10, known to code for cadherin and involved in cell junction organization and ERK signaling. Mutations within CDH10 have previously been reported in colorectal cancer and lung squamous cell carcinoma, but this may be the first implication for prostate cancer.

FIGURE 8. Novel potential actionable therapeutic target for lethal metastatic prostate cancer. A NGM-derived 7Kb somatic deletion was observed to result in almost entire loss of CYP20A1. Cytochrome P450 enzymes are essential for drug metabolism, either inhibiting or inducing drugs. Mutations in these genes are known to impact a patients response to drugs or can direct clinical treatment.

CONCLUSION

Genetic changes are fundamental to prostate cancer progression. Unlike other cancers, complex genomic rearrangements predominate. Detecting these SVs is, however, problematic using current NGS. Using non-sequencing NGM we overcome the limitations of direct sequencing alone. By combining our sequencing and mapping approach, we have identified a novel spectrum of somatic SVs and show added potential of clinical significance for prostate cancer.

Why do we need NGM?

FIGURE 2. NGM and NGS are complimentary.

We demonstrate that NGM (Bionano irys, solid lines) and NGS (Illumina HiSeq Xten, broken lines) are complimentary, rather than competitive, with minimal redundant overlap in detectable SV size distribution.

ACKNOWLEDGMENTS

FIGURE 3. Significant impairment of key genomic interactions in the prostate cancer genome.

Although the greatest number of somatic variants observed in prostate cancer are SNVs (green) (A), by far the largest impact on the tumor genome (total number of bases impacted) includes SVs >1Kb (yellow) (B).