Are we using the right tools to calculate homologous recombination deficiency (HRD) scores?

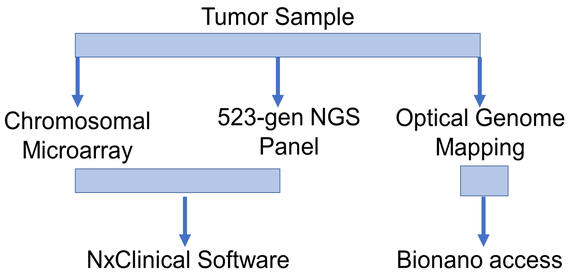
Nikhil S Sahajpal,[1] Ashis K Mondal,[1] Sudha Ananth,[1] Daniel Saul, [2] Andy Pang,[2] Soheil Shams,[2] Alex Hastie,[2] Alka Chaubey,[2] Ravindra Kolhe[1]

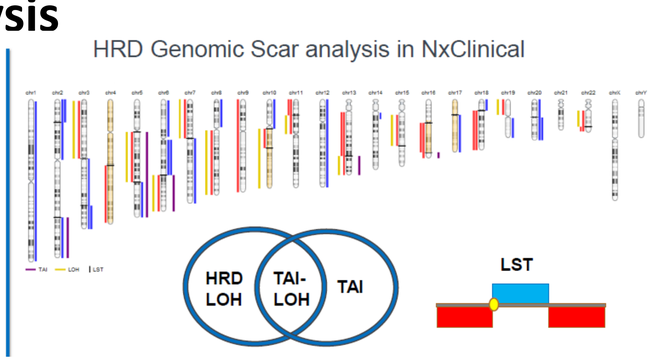
[1]Department of Pathology, Medical College of Georgia at Augusta University, Augusta, GA. [2]Bionano Genomics, San Diego, CA, U.S.A

Introduction

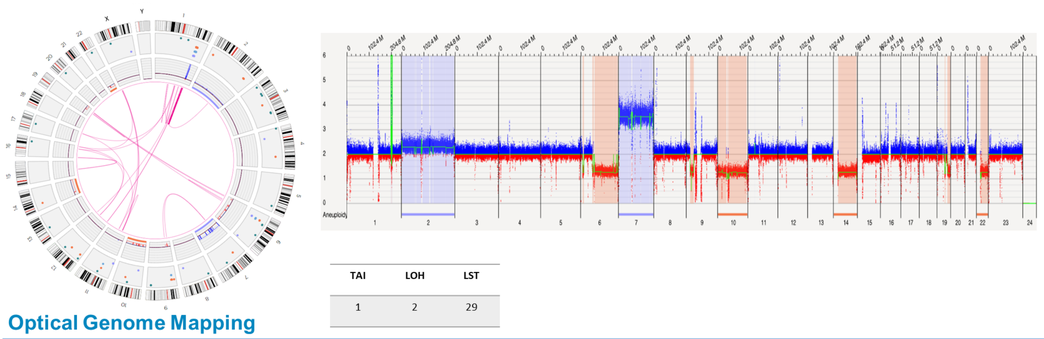
Homologous Recombination Deficiency (HRD) is characterized by the inability of a cell to repair the double-stranded breaks using the homologous recombination repair (HRR) pathway. The deficiency of the HRR pathway results in defective DNA repair, leading to genomic instability and tumorigenesis. The presence of HRD has been found to make tumors sensitive to ICL-inducing platinum-based therapies and poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors (PARPi). However, there are no standardized methods to define, measure, and report HRD in diagnostic laboratories. Herein, we compare optical genome mapping (OGM), chromosomal microarray (CMA), and 523-gene NGS panel for HRD scar calculations.

Samples and Data Analysis



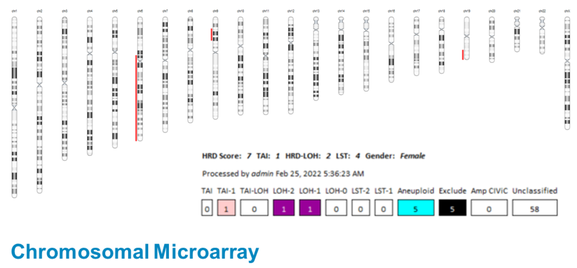


Comparison of OGM with CMA

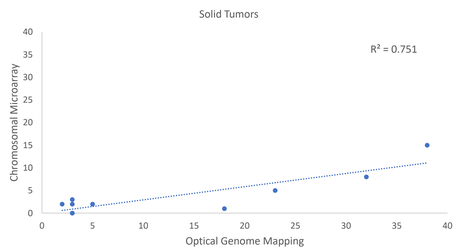


Optical Genome Mapping

TAI	LOH	LST
1	2	29

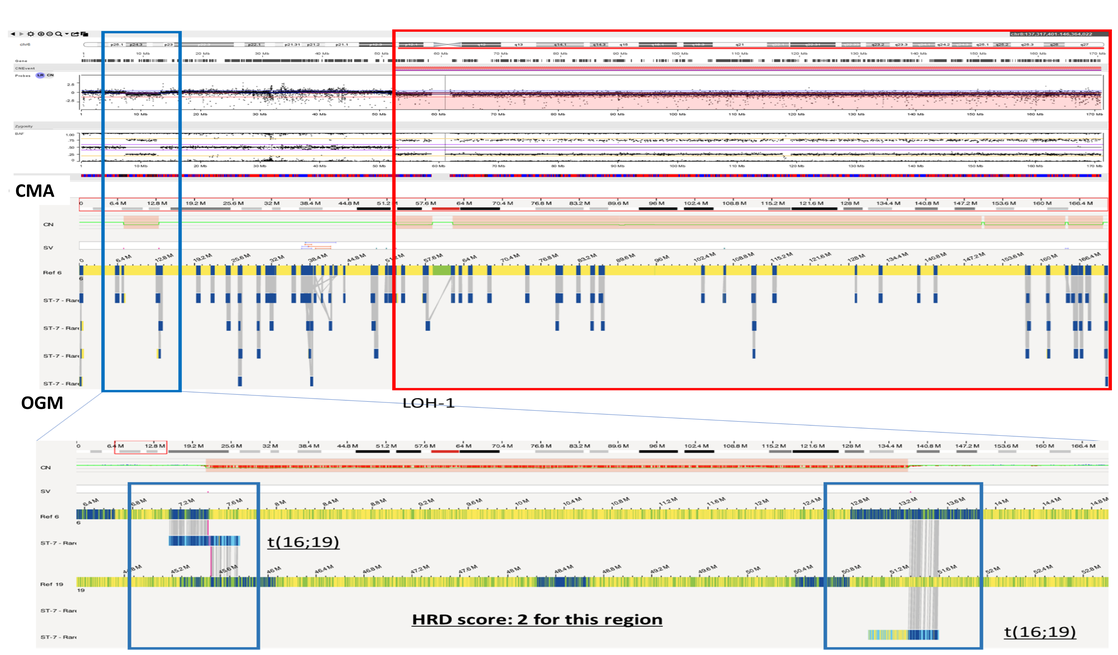


Chromosomal Microarray



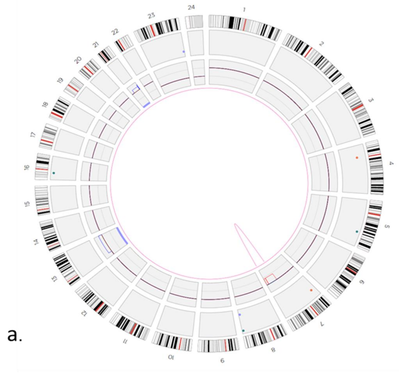
Comparison of HRD scores between OGM and CMA in Gliomas

In the ten glioma cases analyzed with OGM and CMA using the same DNA, the HRD scores were 13 (±13.7) with OGM compared to 3.7 (±4.5) with CMA. OGM missed two absence of heterozygosity regions in one case. OGM detected 70.8% additional structural variants that resulted from HRD, which included translocations, inversions, and fusions.



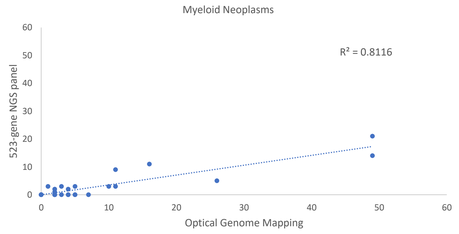
Red box: Shows a >15 Mb copy number loss including telomere and centromere, resulting in LOH-1 (HRD score=2). Blue box: Shows a <10 Mb copy number loss, which did not add to HRD score (HRD score=0) with CMA. However, the 5.3 Mb deletion resulted from translocations t(16;19) at both breakpoints and resulted in a HRD score of 2 with OGM

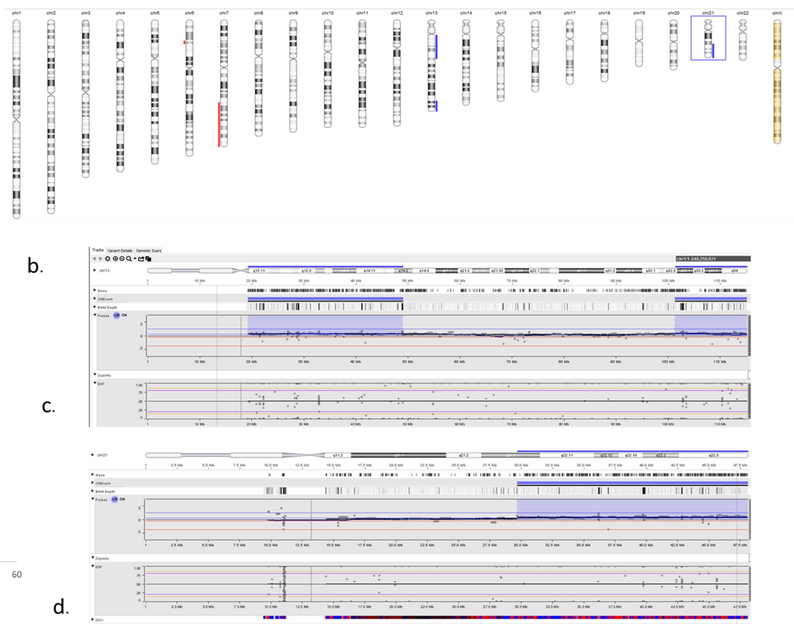
Comparison of OGM with NGS Panel



a.

Myeloid Neoplasms

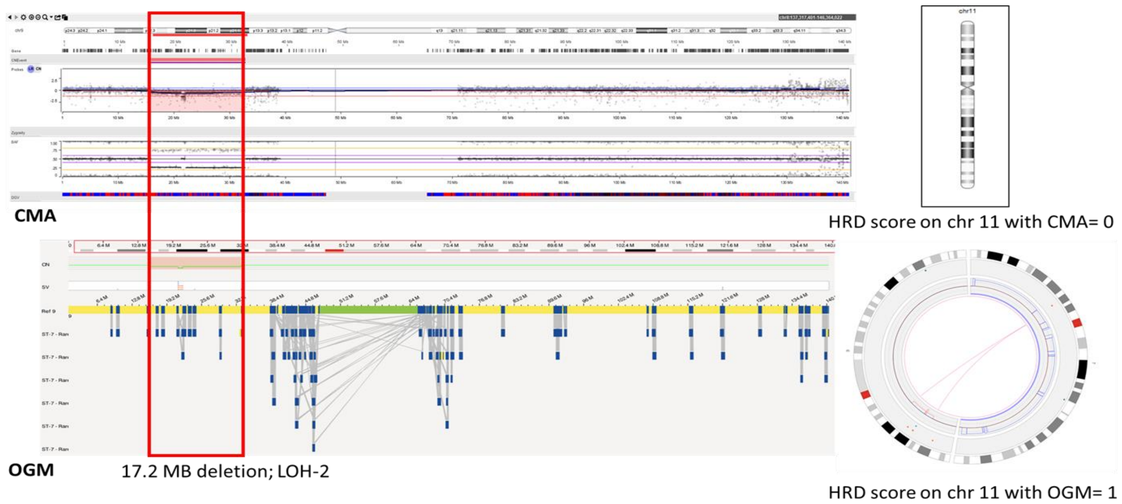




b. c. d.

Comparison of HRD scores between OGM and 523-gene NGS panel in Myeloid Neoplasms

In the 32 myeloid neoplasm cases analyzed with OGM and 523-gene NGS panel, the HRD scores were 6 (±10.5) with OGM compared to 2.1 (±4.3) with 523-gene NGS panel. OGM detected 65% additional structural variants that resulted from HRD.



Left panel shows the comparison of OGM with CMA an HRD scar, LOH-2 (>15 Mb deletion) that contributed a score of 3 with CMA and 4 with OGM as the deletion was part of a translocation t(9;11). Right panel: Shows a large (>10 Mb) inversion with OGM that contributes a score of 2 towards HRD calculation.

Conclusion

The current literature highlights the is high variability in the platforms and the definition of HRD scars. In this phase when several clinical trials are underway or are being initiated, it is necessary to use the most sensitive tools that can capture the phenotype accurately. This study highlights the HRD scars that are missed by current technologies used for accessing HRD phenotype, and presents OGM as an alternative tool with high resolution and sensitivity to accurately assess the HRD phenotype.