

Whole Genome Sequencing

As described in Chaubey et al., Journal of Molecular Diagnostics, vol. 22, No. 6 June 2020, they used 10x WGS and validated that the N_xClinical algorithm detected all CNVs and AOH that were found by high resolution SNP arrays. Figure 2. shows a small exonic deletion detected using 10x WGS with the MSR algorithm.

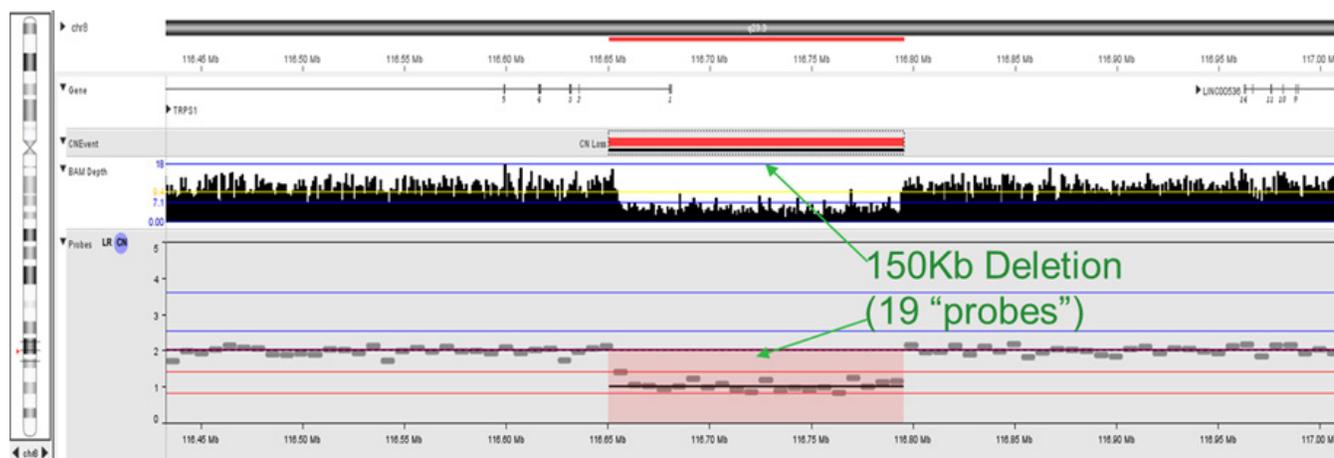


Figure 2. A deletion on chromosome 8 which includes the first exon of TRP51 is shown along with the BAM depth.

With higher depth NGS, smaller CNVs can be detected and integrated with sequence variants to provide a wholistic view of the sample. In Figure 3, the ideogram shows regions of copy number gain (blue bars), loss (red bars), AOH (yellow shading), Allelic Imbalance (purple shading), as well as various types of Sequence Variants (e.g., SNV, In/Del, etc.) as colored "lollipops".

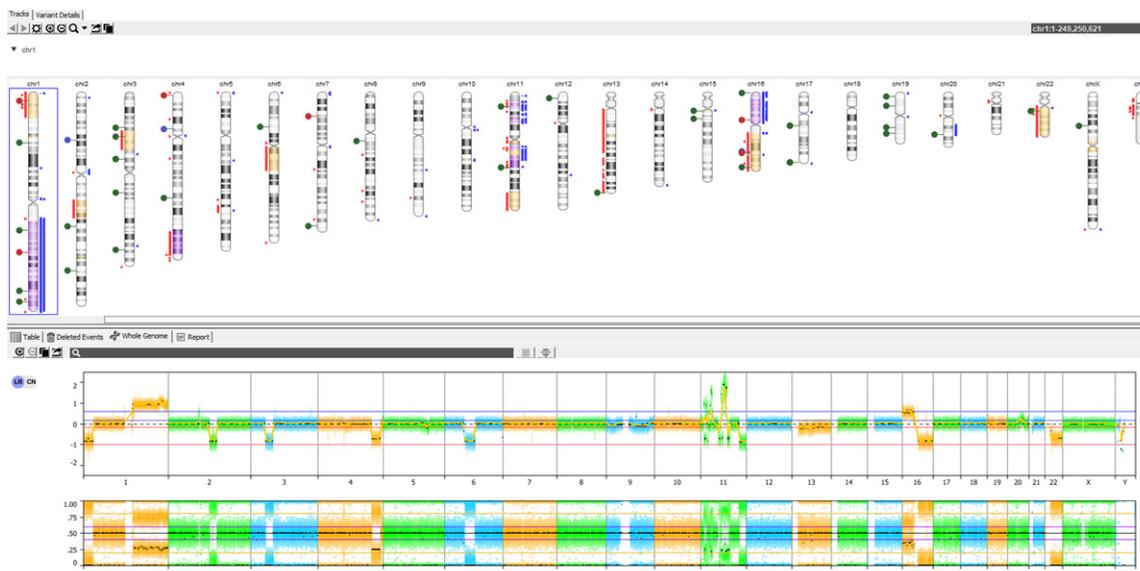


Figure 3. Whole genome view in N_xClinical. The top shows the cytogenic view in an ideogram of all of the chromosomes overlaid with CN loss (red), CN gain (blue), AOH (yellow highlight), and Sequence Variants (lollipops) and the bottom shows the molecular view of the whole genome in log ratio and B allele frequency plots.

Gene Panels

The MSR algorithm can be applied to any gene panel from single gene (e.g. DMD test) to large panels having thousands of genes. Figure 4 below is from the Illumina TruSight™ Oncology 500 (TSO500) panel showing a somatic cancer profile. The cytogenetic complexity of the tumor sample is clearly evident with a large copy number gain of 8p and loss of a large section of 13q. Aberrations associated with genomic scarring, such as Loss of Heterozygosity (LOH), telomeric allelic imbalances (TAI), and large-scale state transitions (LST) can be visualized and manually called with confidence.

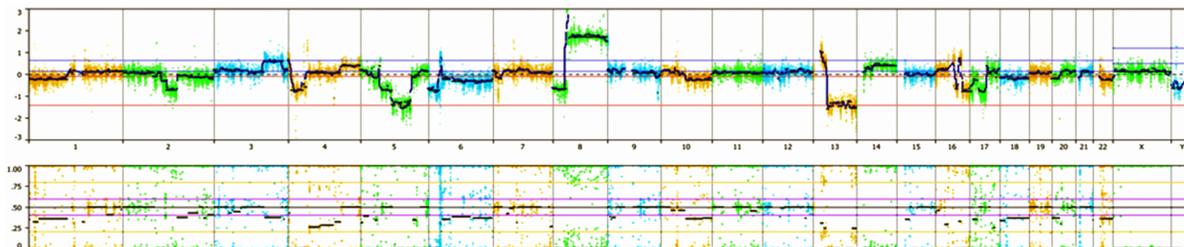


Figure 4. Shows the log R whole genome view of TSO-500 panel in NxClinical. By using a virtual probe strategy, NxClinical gives a much richer view of the whole genome than would be expected by a 500 gene panel.

Shallow Sequencing

The MSR algorithm can also be applied to detect CNVs from shallow sequencing, including very low-level mosaic events seen in NIPS or ctDNA samples. Figure 5 shows a sample with trisomy 21 detected using 1x WGS. CNVs are an important contributor to disease and are required for accurate reporting. For clinical sequencing to be fully accepted as a replacement for microarrays and other widely used techniques, it must provide high quality CNV information. NxClinical can easily and accurately provide that information from various approaches using NGS data.

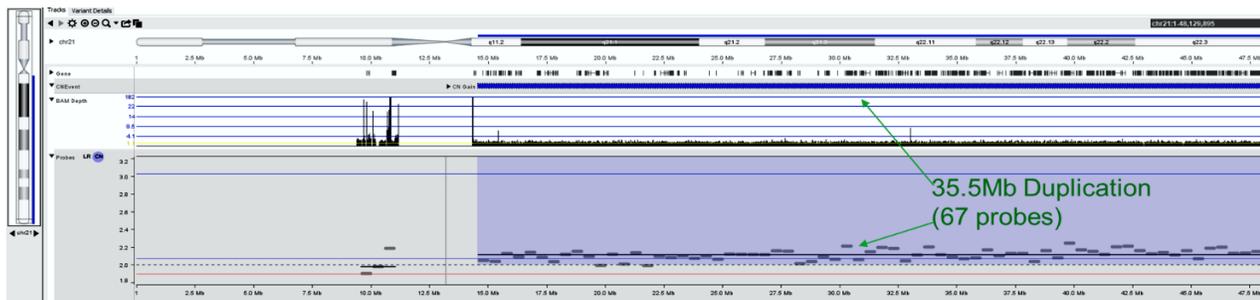


Figure 5. A large duplication event affecting the q arm of chromosome 21.

For general information about NxClinical, please contact

+1 310.414.8100

info@bionano.com

bionano.com

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