Visualizing Different Classes of Structural Variants in Bionano Access Software

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Revision History

Revision	Notes
A	Initial Release

1. OVERVIEW

1.1. Bionano Access® Software enables users to view Saphyr® run results in real time, perform a variety of bioinformatics analyses, and visualize structural variation (SV) that has been detected through optical genome mapping (OGM). This reference document guides users through data visualization by variant class. It covers numerous examples of different SV classes and other variant classes detectible by OGM, including insertions, deletions, duplications, inversions, translocations, ring chromosomes, complex rearrangements, absence of heterozygosity (AOH), and triploidy. The purpose of this reference document is to help answer user questions and clarify user results, and to organize data into information meaningful to the user. **NOTE**: OGM can detect variation throughout most of the genome but does not include coverage of centromeres, short arms of acrocentric chromosomes, and some exceptionally long paracentric low copy repeat regions.

2. DISTINCT DATA VISUALIZATION METHODS

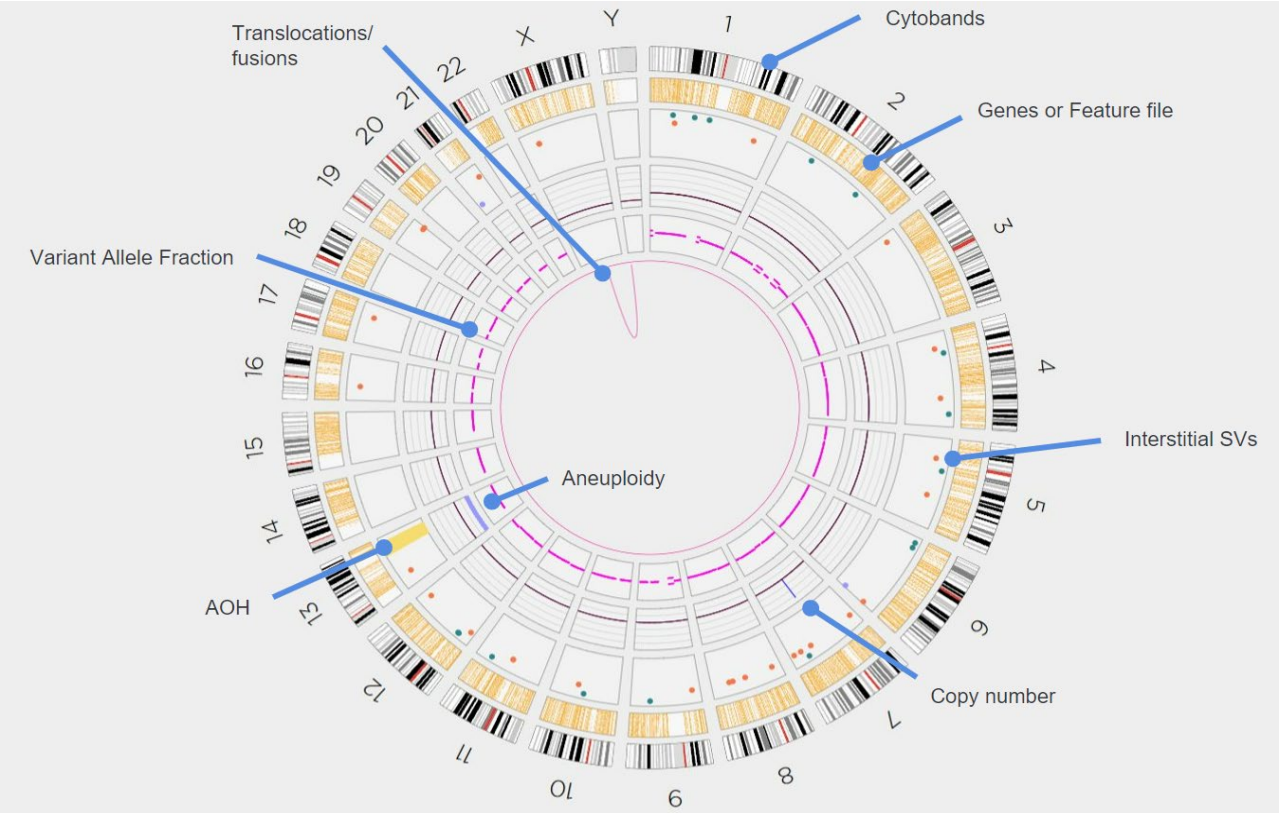


Figure 1: General Circos Plot

2.1. In **Figure 1**, the Circos plot provides a whole genome summary of variants detected: copy number (CN) state, regions of absence of heterozygosity (AOH), and a variant allele fraction profile. This

display is filtered dynamically in the user interface of the Access software. The Circos plot also displays chromosome number, cytobands, and, optionally, gene locations. For more details, please refer to the *Bionano Access Software User Guide* (P/N 30142) or to the Bionano Support website.

2.2. Genome Browser

2.2.1. There are two algorithm sets for whole genome structural variation detection: the De Novo Assembly pipeline and the Rare Variant Analysis pipeline (RVA). The De Novo Assembly pipeline is primarily for germline variants and the RVA is primarily for somatic variants.

2.3. De Novo Assembly Pipeline

Figure 2: Genome browser – De Novo Assembly pipeline

2.3.1. In **Figure 2,** the genome browser displays alignment of all assembled maps on single chromosomes. In this example, maps from the De Novo Assembly pipeline are shown. This pipeline generally assembles contiguous maps, up to chromosome arm length. **NOTE**: the default color for non-matching labels is yellow but it can be changed as it has been here, in red, for better resolution and contrast.

The top header displays the types of views, locations on the chromosomes, and customizable options. The top ruler and cytoband track depict what part of the chromosome is being displayed (outlined in red in this example). Cytobands are shown as alternating white, gray, or black bands, with red bands representing centromeres. Other items include:

- CN – track showing copy number baseline, datapoints, and CNV calls
- SV – track showing structural variants
- Gene/feature file – when loaded on the Circos plot view, presents BED files containing known hg19 canonical genes
- Reference chromosome – Ref 1, in this image
- Sample maps that are aligned to the reference
- Bottom pane - Variant Annotation tables

2.4. Rare Variant Analysis Pipeline

Figure 3: Genome browser – Rare Variant Analysis pipeline

2.4.1. In **Figure 3**, the genome browser presents the output of the RVA pipeline. The molecules from regions of the genome containing SVs are assembled into maps and each map generally represents a single SV or a cluster of SVs, indicated by the blue pointer. No map is created for parts of the genome matching the reference, hence there are “gaps” with no maps. Here, red colored segments of maps (default color is yellow) indicate that the region is not aligned to an assembled map and the user can infer that there is no SV present.

2.5. Whole Genome Copy Number Variant (CNV) View

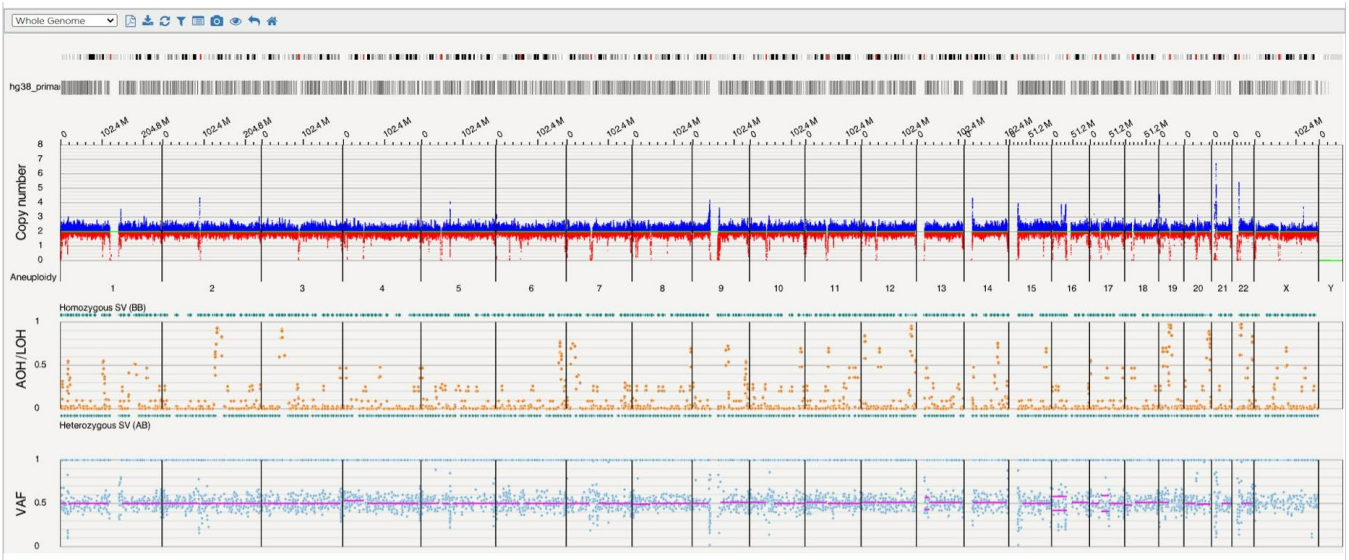


Figure 4: Whole Genome CNV

2.5.1. The whole genome view (top plot) can display the copy number profile calculated by the CNV algorithm based on the number of molecules aligned to the reference genome, as seen in **Figure 4**. This plot highlights CN datapoints centered around a baseline of CN=2, with CNV calls where regions have higher or lower copy coverage compared to most of the genome (generally regions of >500 kbp). The middle plot shows the zygosity of SVs and AOH/LOH data and calls. The final plot on the bottom shows the variant allele fraction (VAF) for each SV. For more detailed information please refer to the *Bionano Access Software User Guide* (P/N 30142) or to the Bionano Support website.

3. VARIANTS BY CLASS

3.1. **Aneuploidy**

3.1.1. Aneuploidy is defined as the condition of having an abnormal number of chromosomes in a diploid cell. For a detailed description of how aneuploidy is called from OGM data, please see the Bionano Genomics document *Bionano Solve Theory of Operations: Structural Variant Calling* (P/N 30110).

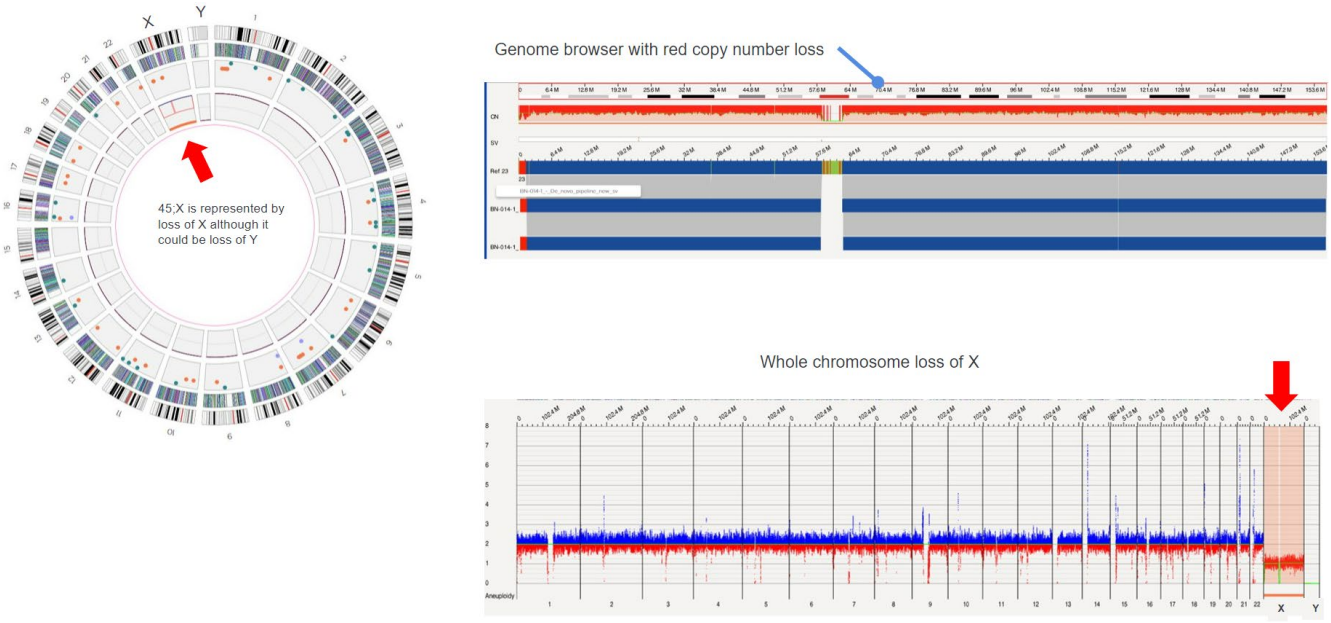


Figure 5: Monosomy – ogm[GRCh38] (X)x1

3.1.2. As shown in **Figure 5**, monosomy, where a single chromosome is represented, can be detected by the CNV algorithm, visualized on the Circos plot as an orange bar in the inner ring (red arrow in this example), and as a copy number call in the first ring (thin red segment(s) inward from the CN baseline). Monosomy can be visualized in the genome browser as red shading and darker red lines projecting down from the top. The whole genome view also indicates loss of chromosome in the same way as the genome browser does. This example shows a 45;X chromosome count which could indicate a loss of X or a loss of Y; the loss of X is arbitrarily indicated as default.

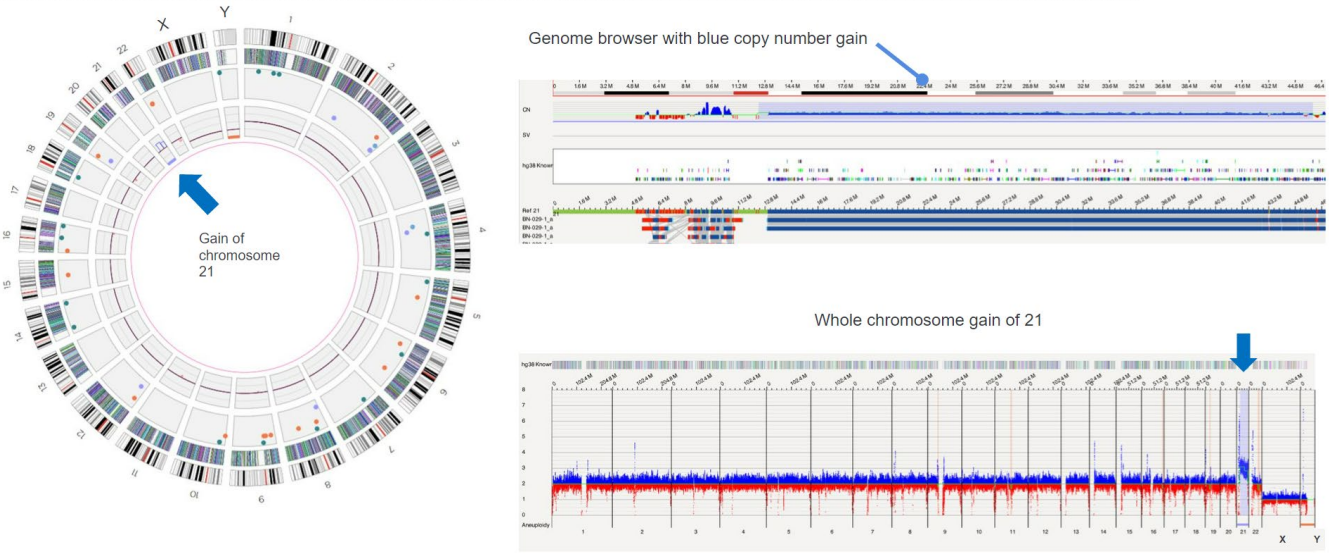


Figure 6: Trisomy – ogm[GRCh38] (21)x3

3.1.3. Trisomy, where three chromosomes are represented, can be detected by the CNV algorithm, visualized on the Circos plot as a lavender bar in the inner ring (blue arrow on Circos plot), and as a CN call in the first ring (thin blue line), as shown in **Figure 6**. It can be visualized in the genome browser as blue shading and darker blue lines projecting up from the CN status of two. The whole genome view also indicates the gain in the same way as the genome browser does. Since OGM does not detect acrocentric short arm fusions, this profile could represent a true trisomy or an unbalanced Robertsonian translocation.

3.2. Copy Number Variants: Deletions

3.2.1. Copy number variation refers to a circumstance in which the number of copies of a specific segment of DNA varies among different individuals' genomes. The individual variants may be short or include thousands of bases. These structural differences may have come about through duplications, deletions or other changes and can affect long stretches of DNA. Such regions may or may not contain a gene(s).

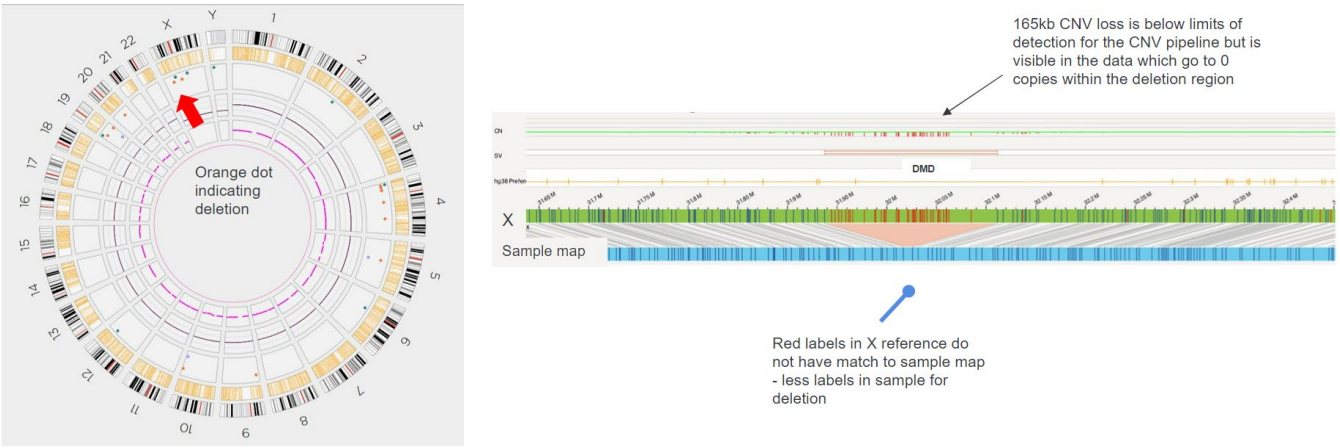


Figure 7: Interstitial deletion – ogm[GRCh38]Xp21.1(31937331_32111402)x0

3.2.2. The deletion in **Figure 7**, depicted in this image by the orange dot, is not called in the CNV pipeline but it *is* visible in the data. It is not called due to size (165kbp) as the performance of the CNV caller is measured and reported for events 500kbp and above. An interstitial deletion can be seen in the Circos plot as an orange dot, in the genome browser as an SV call (red triangle), and as a horizontal red bar in the SV track. The loss is not called by the CNV algorithm but is supported by the red lines in the CN track.

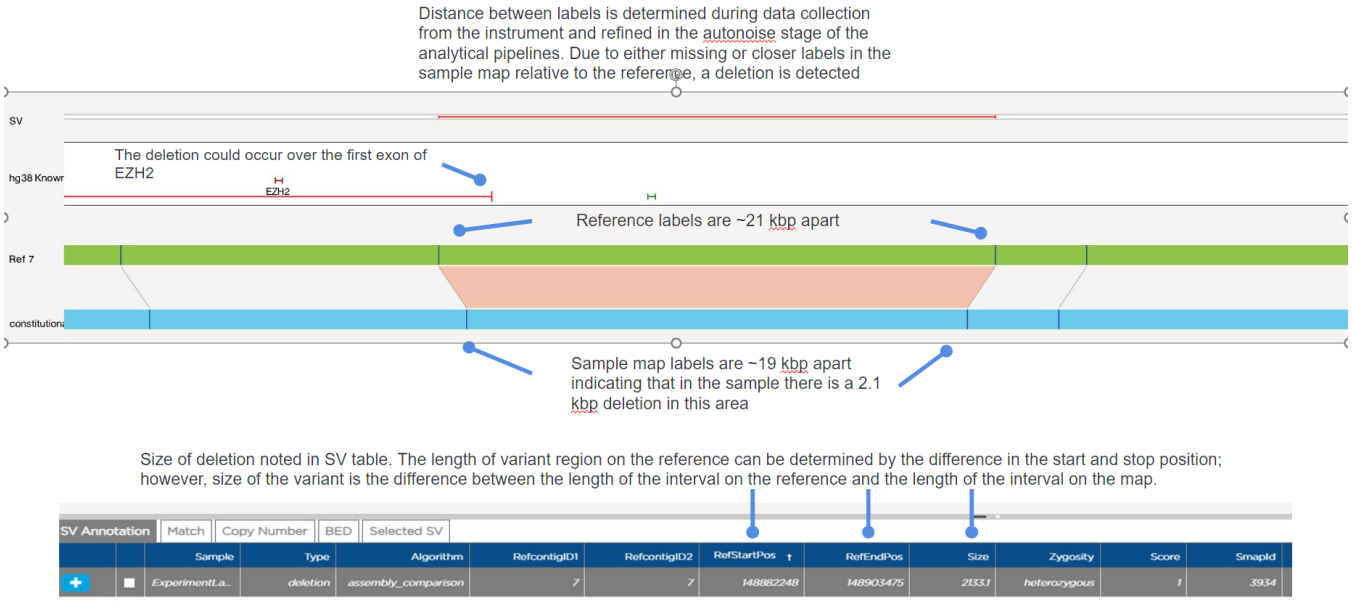


Figure 8: Schematic to illustrate how deletion size is calculated from the difference between the reference and sample inter-label distances.

3.2.3. Determining the size of the deleted/inserted region is calculated by measuring the distance between two labels in the sample and finding the difference with the

corresponding reference labels. **Figure 8.** Unlike a chromosomal microarray, OGM gives the position of the outermost markers while also providing a precise size for the deletion or insertion; the uncertainty pertains to exactly where the deletion is within the window. Refer to the *Theory of Operations: Structural Variant Calling* (P/N 30110) document, Appendix D, for more information.

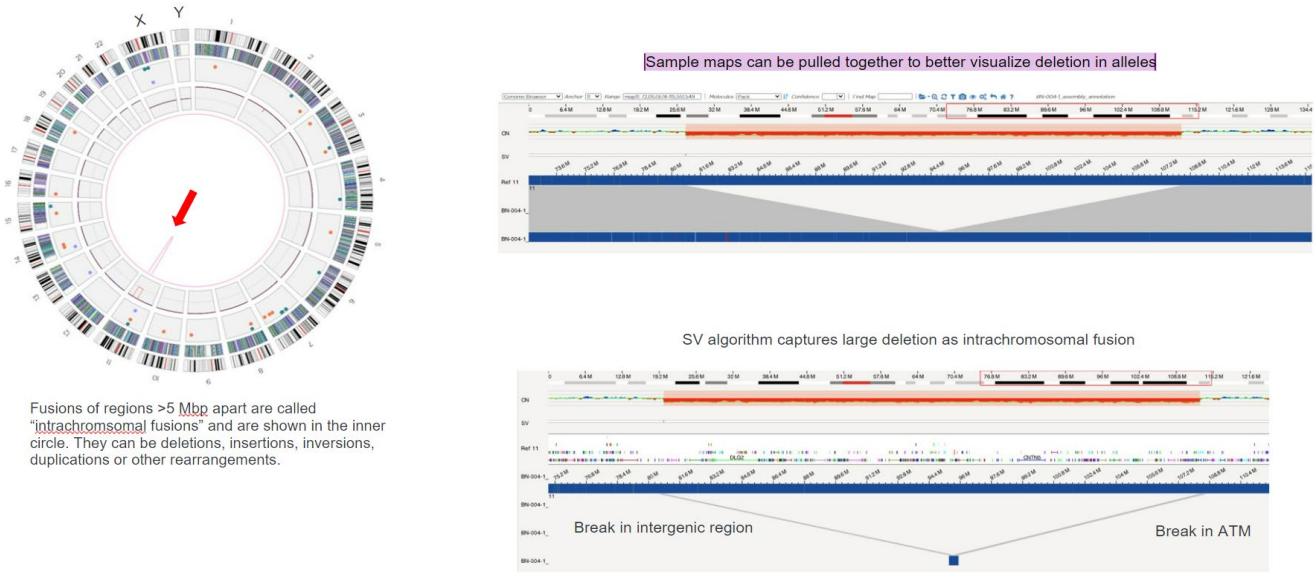


Figure 9: Large deletion – ogm[GRCh38] 11q14.1q22.3(80770323_108306632)x1

3.2.4. Large deletions can be seen in the Circos plot in **Figure 9** as a red arrow and connecting lines between sides of the deletion. In the genome browser, large deletions are visualized as a red bar in the CNV track and an intra-chromosomal fusion (if >5 Mbp, or as a deletion if smaller than 5 Mbp) in the SV track.

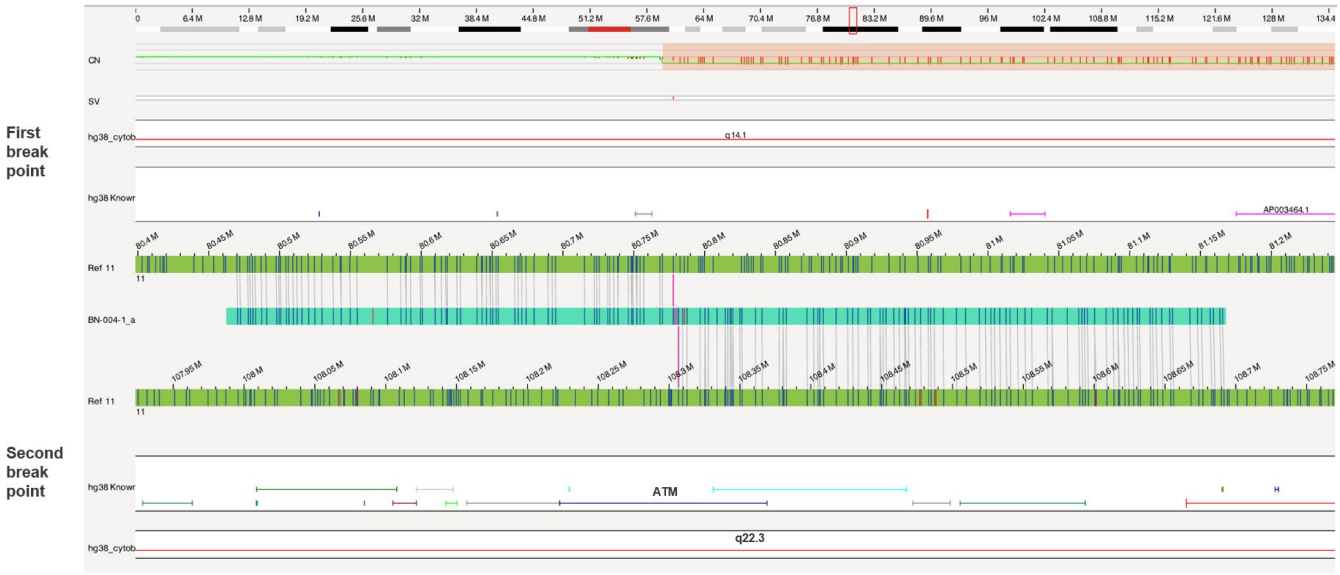


Figure 10: Fusion map from deletion – ogm[GRCh38] t(11;11)(q14.1;q22.3)(80770323_108306632)

3.2.5. By selecting the intra-chromosomal variant from the annotation table, a fusion map depicts both sides of the deletions, visualized vertically in **Figure 10**.

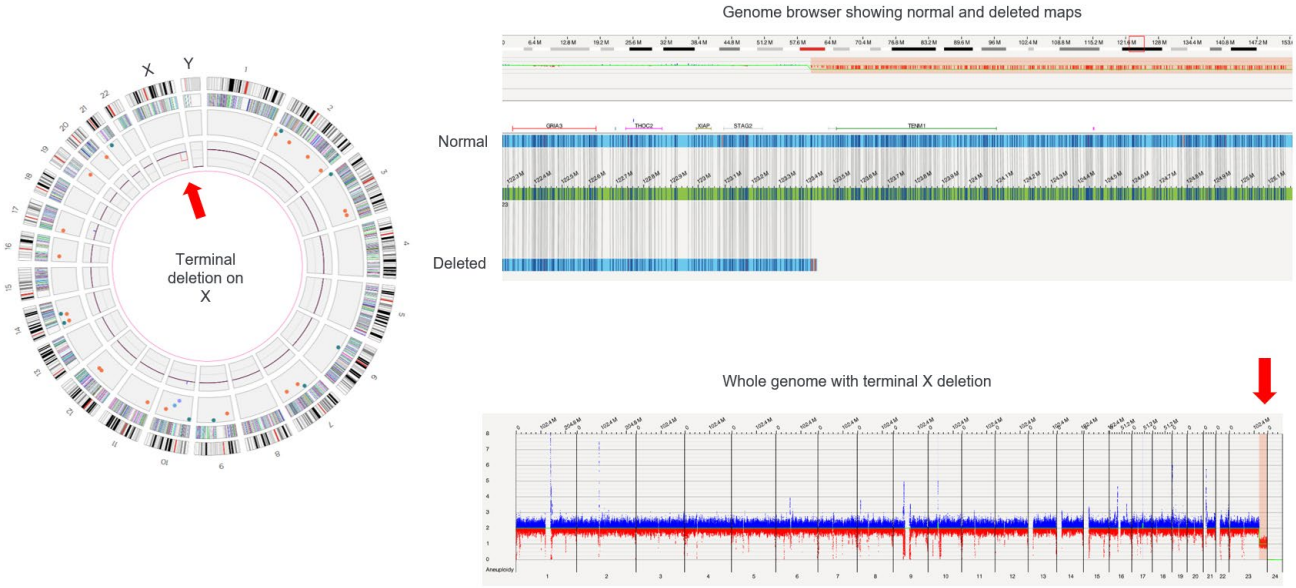


Figure 11: Terminal deletion - ogm[GRCh37] Xq25q28(123414783_155255277)x1

3.2.6. In **Figure 11**, the terminal deletion was detected by the copy number algorithm. However, there is no map that can flank both sides of the deletion, so the SV algorithm was unable to call the deletion. Please refer to the *Bionano Solve Theory of Operations: Structural Variant Calling* document (P/N 30110) for more details.

3.3. Copy Number Variants: Duplications

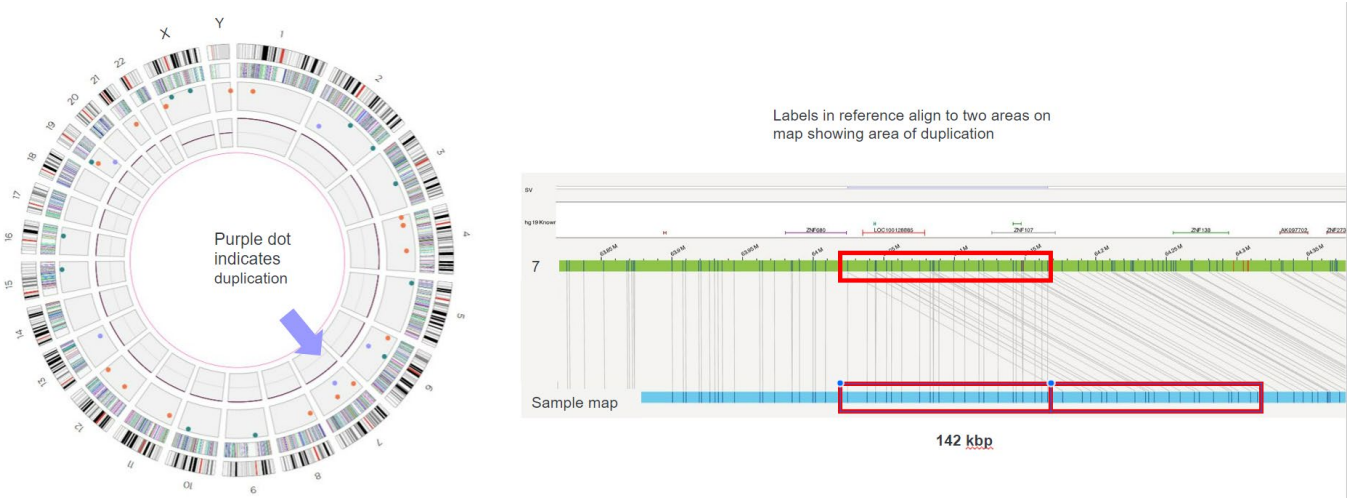


Figure 12: Tandem duplication - ogm[GRCh37] 7q11.21(64024489_64166043)x3

3.3.1. Duplications are indicated by the purple dots in the SV track of the Circos plot in **Figure 12** and by maps with double alignment to the reference in the genome browser. In this example, a tandem direct duplication based on the location adjacent to the first copy and in the same orientation is displayed.

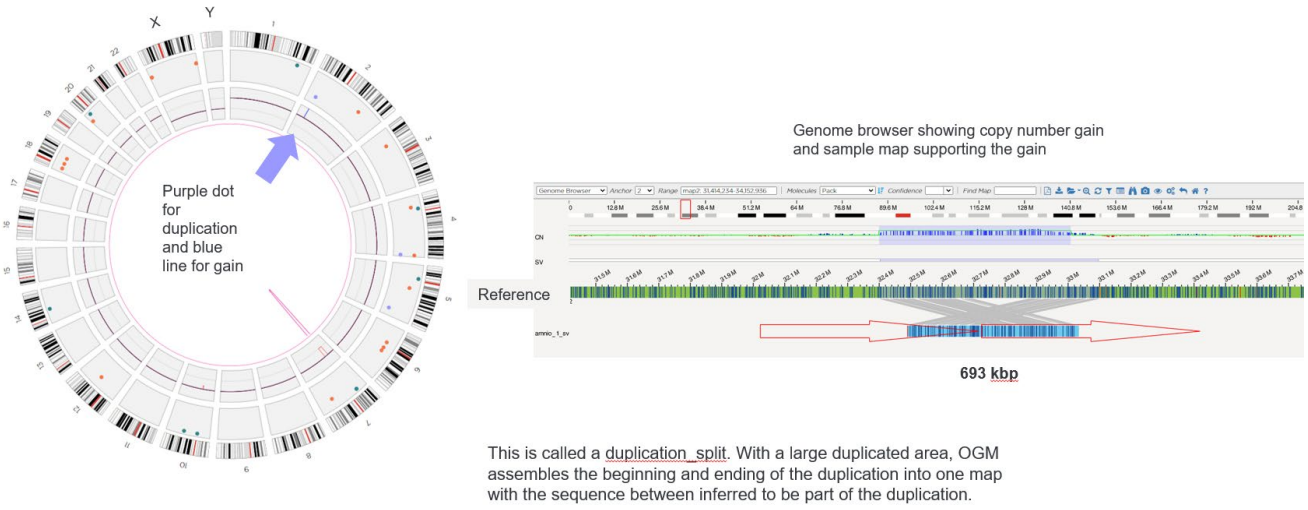


Figure 13: Large duplication - ogm[GRCh38] 2p22.3(32403156_33096390)x3

3.3.2. In **Figure 13**, duplications large enough to be called by SV and CNV algorithms are indicated in the Circos plot as a purple dot in the SV track and blue lines in the copy number track. In the genome browser, large duplications are visualized as a blue bar in the CNV track and a duplication split map in the SV track. Tandem duplications larger than 2 Mbp are called as “intrachromosomal fusions” and as blue CNV increase calls (not shown).

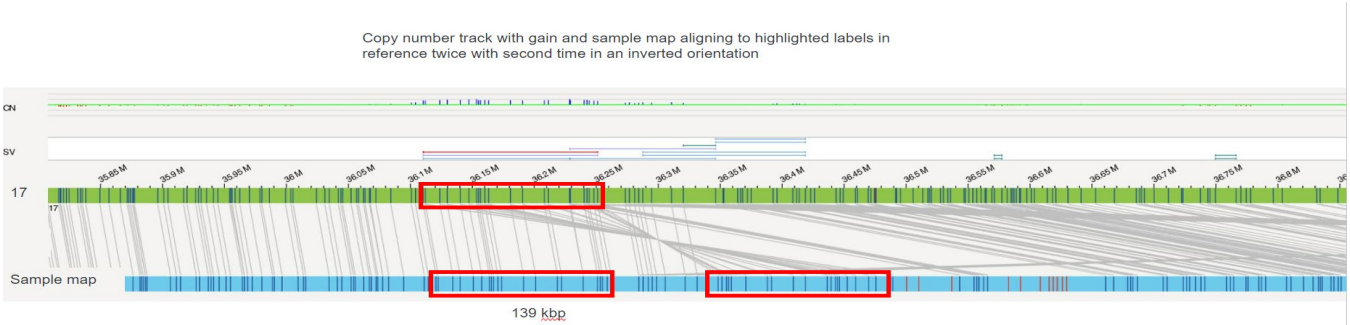


Figure 14: Inverted duplication - ogm[GRCh38] 17q12(36112148_36251175)x3, ogm[GRCh38] inv(17)(q12)(36112148_36251175)

3.3.3. Inverted duplications are shown in **Figure 14** as inverted, duplicated alignments to the reference map.

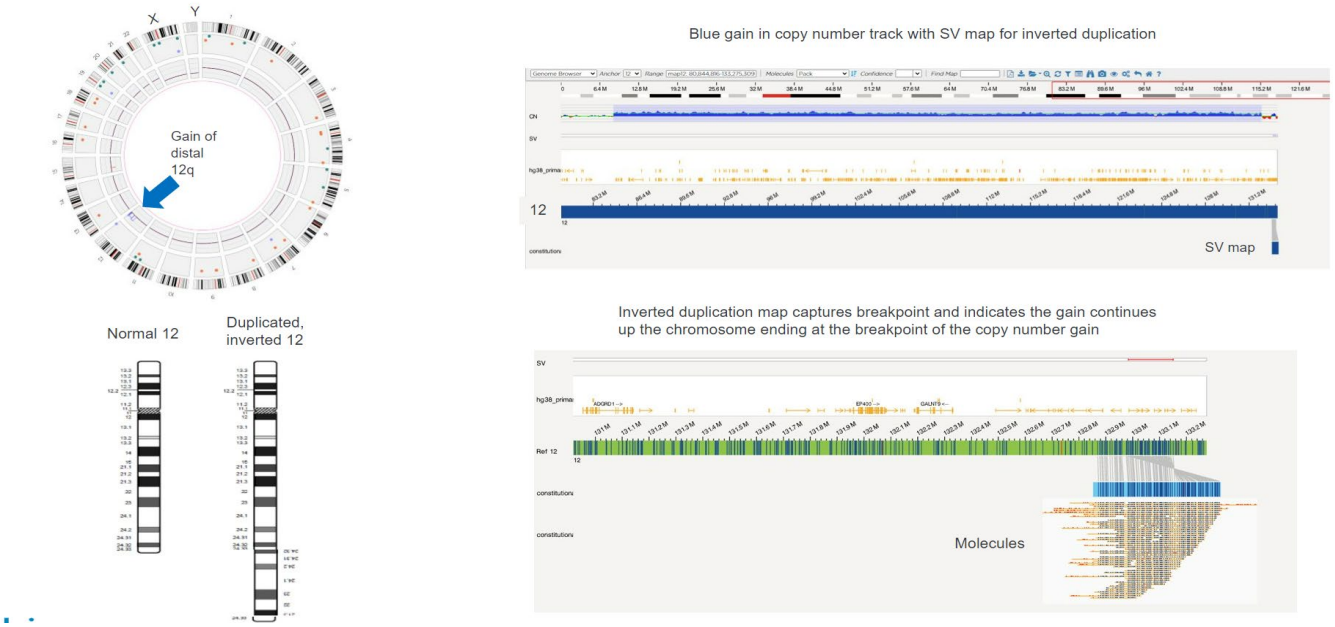


Figure 15: Terminal inverted duplication - ogm[GRCh38] inv(12)(q21.31q24.33)(84677954_133150659)x3

3.3.4. In the Circos plot in **Figure 15**, terminal inverted duplications are shown as lavender dots in the SV track and blue lines in the copy number track. In the genome browser, the variant is represented by a blue bar in the copy number track and by an SV map that contains a duplicated, inverted alignment. The SV map may not extend sufficiently to span the duplicated region, as inverted duplications may be indicative of foldback junctions.

3.4. Structural Variants: Insertions

3.4.1. Historically, structural variation is generally defined as a region of DNA approximately 1 kbp and larger in size and can include inversions and balanced translocations or genomic imbalances in the presentation of insertions. However, since the sequencing of human genomes has become routine, the operational spectrum of SVs and CNVs has widened to include smaller events (for example, those >50 bp in length).

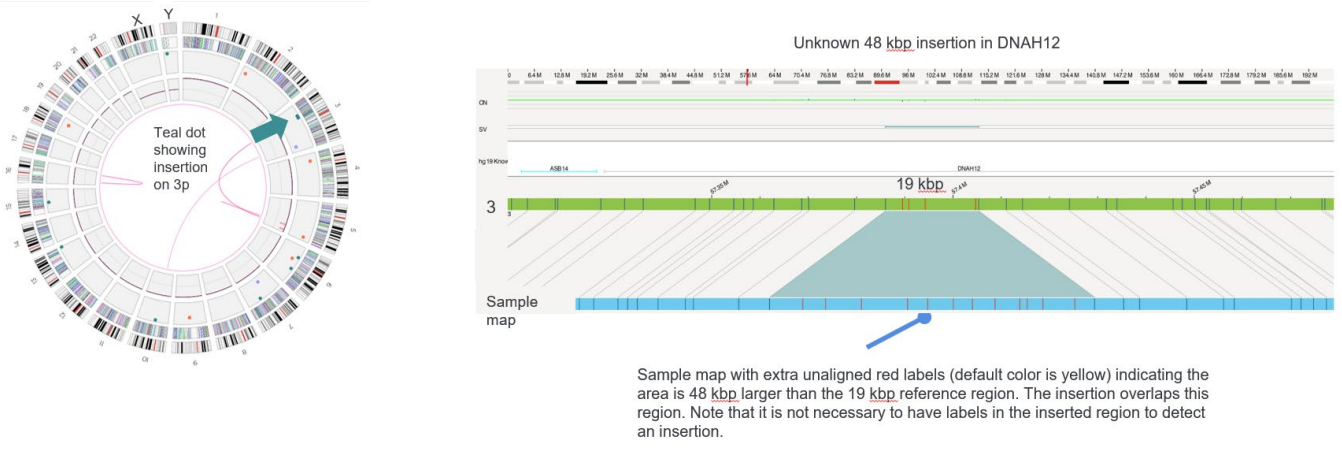


Figure 16a: Insertion - ogm[GRCh37] ins(3)(p14.3)(57386006_57405344)

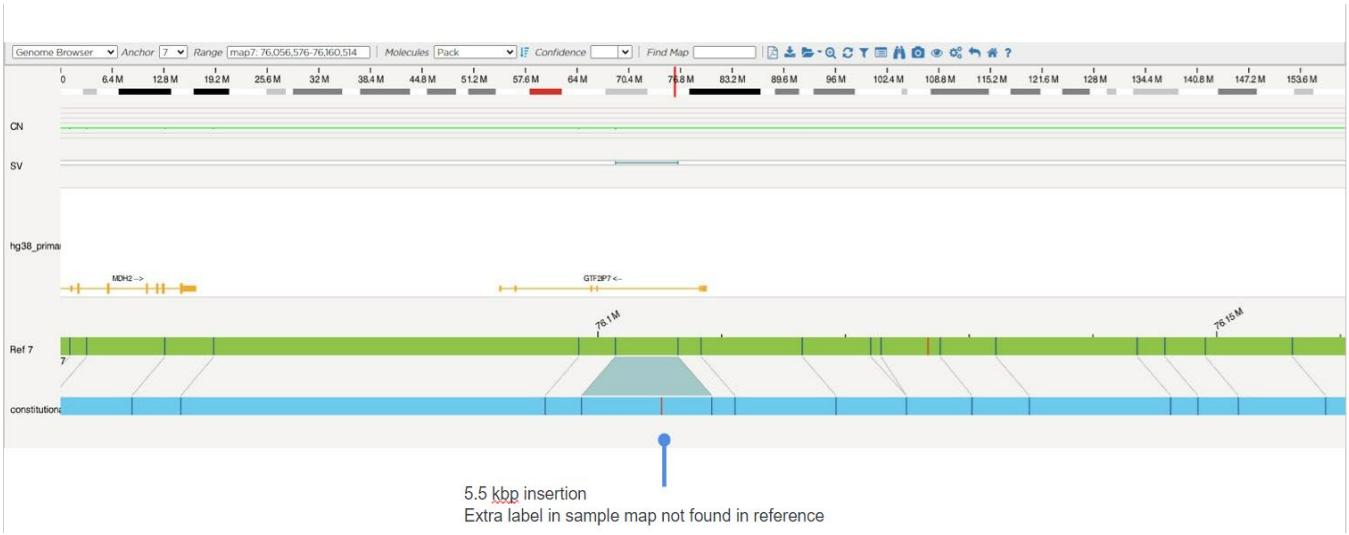


Figure 16b: Small insertion of unknown origin – ogm[GRCh38] ins(7;?)(q11.23;?).

3.4.2. In **Figures 16a and b**, insertions are represented by teal dots in the SV track and by maps that contain boundary labels larger than the reference positions in the genome browser.

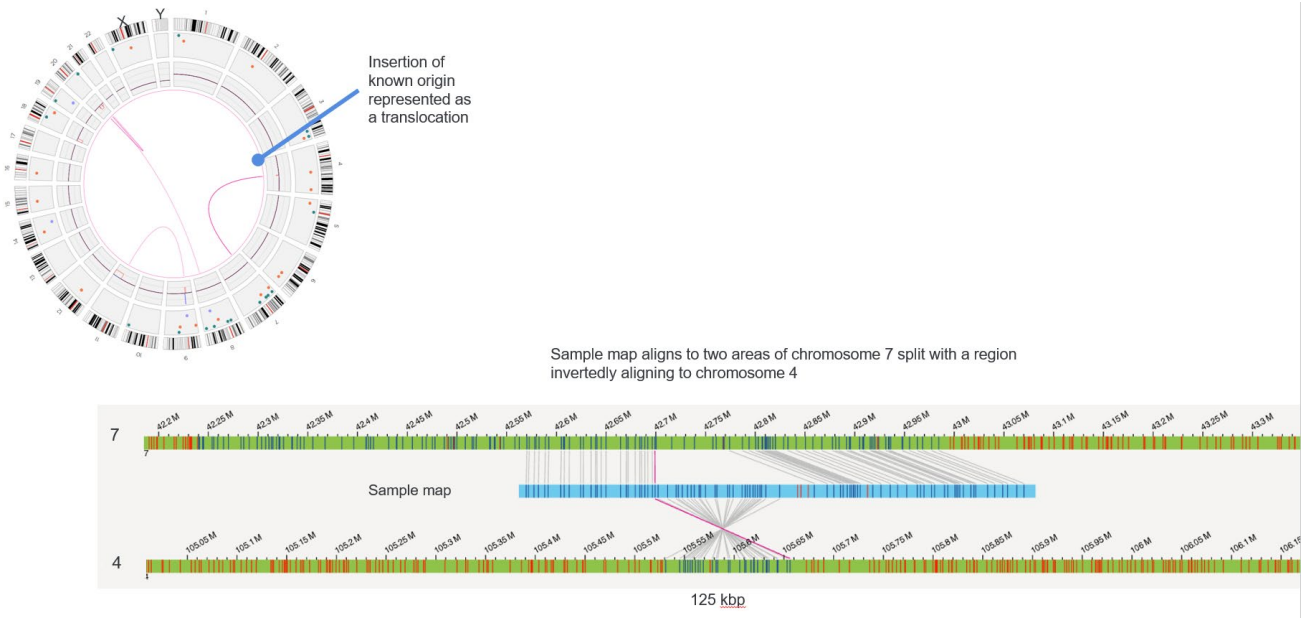


Figure 17: Insertion with known genetic origin - ogm[GRCh38] inv ins(7;4)(p14.1;q24)(42699099; 105656151_105531076)

3.4.3. Insertions of known origin are indicated by magenta translocation lines in the Circos plot in **Figure 17** and by translocation maps in the genome browser.

3.5. Structural Variants: Translocations

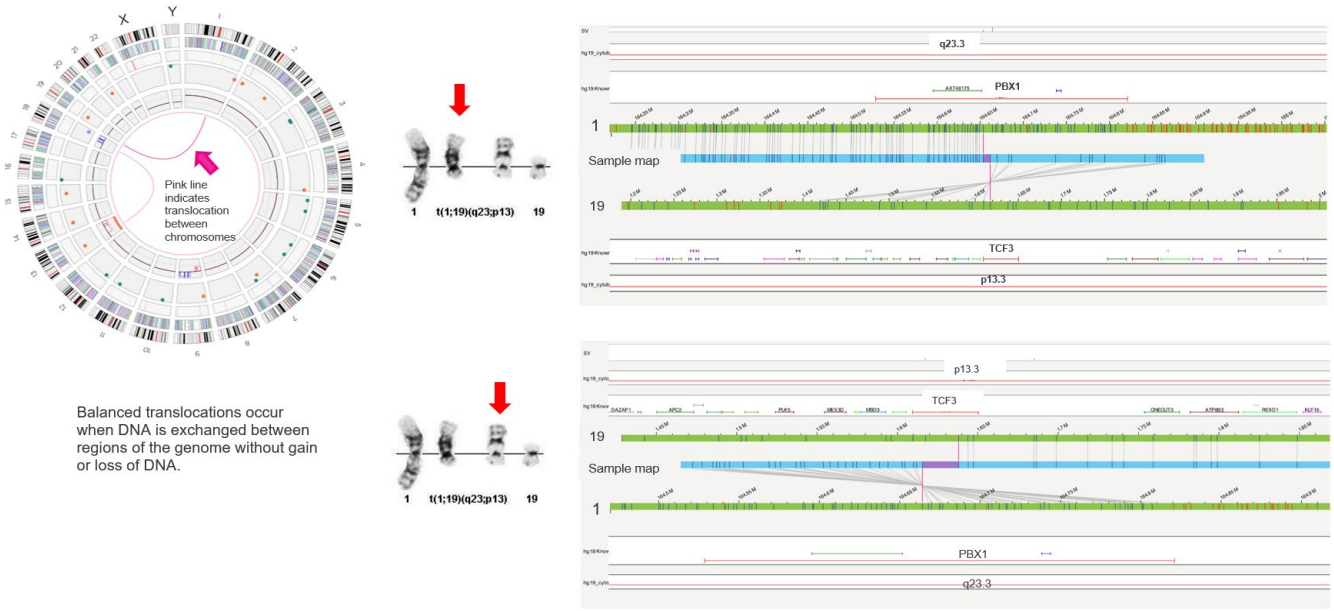


Figure 18: Balanced - ogm[GRCh37] t(1;19)(q23.3;p13.3)(164653451_1617441)

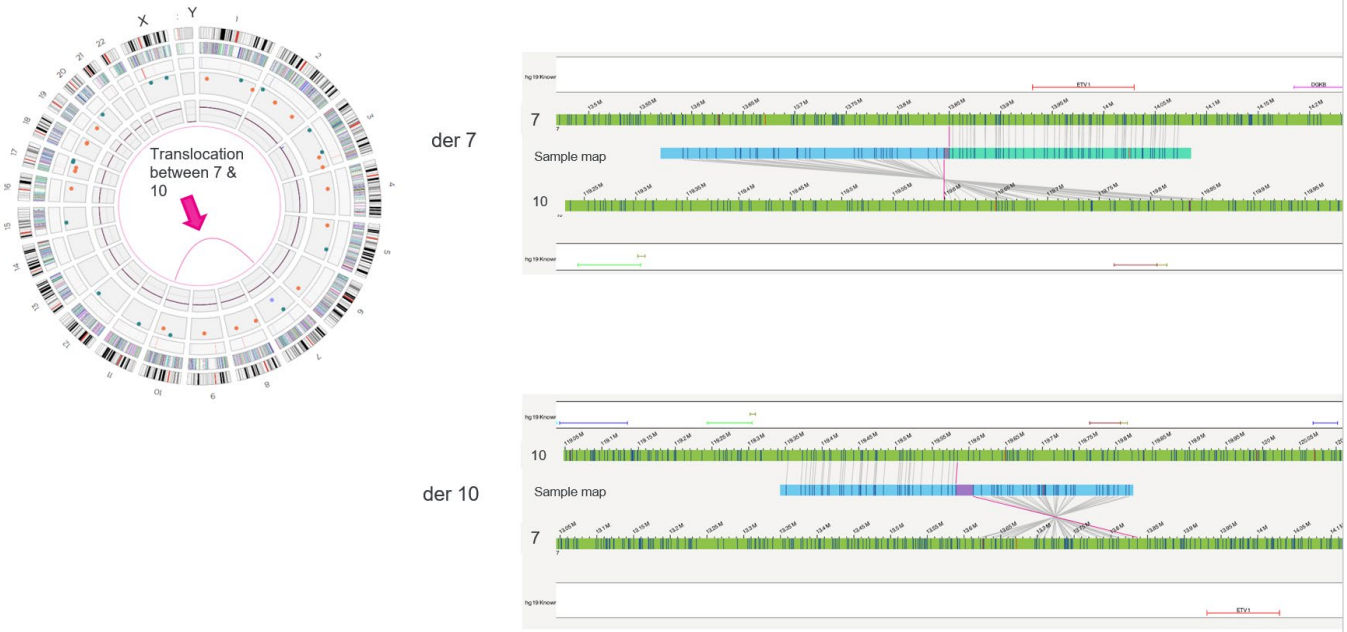


Figure 19: Balanced - ogm[GRCh37] t(7;10)(p21.2;q26.11)(13850028_119599351)

3.5.1. **Figures 18 and 19**.In both Circos plots above, balanced translocations are indicated by magenta lines connecting the involved chromosomes. Breakpoints and genes can be visualized in the genome browser by viewing the translocation maps.

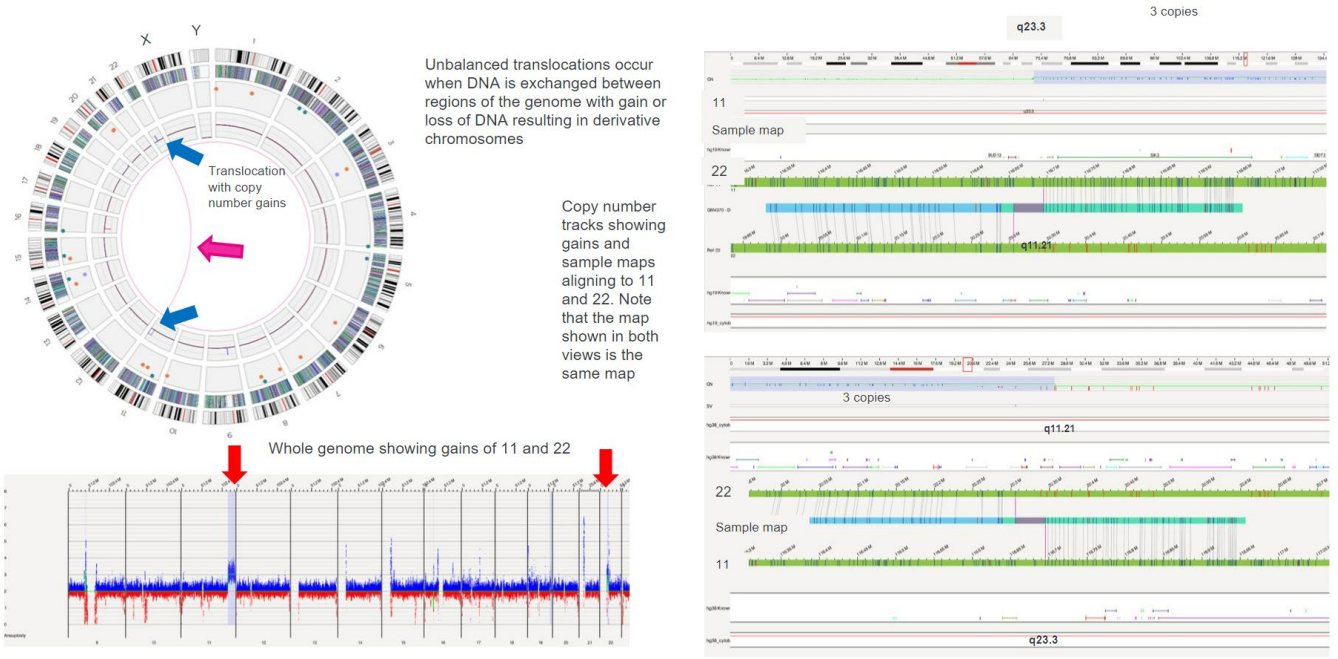


Figure 20:Unbalanced translocation - ogm[GRCh37] t(11;22)(q23.3;q11.21)(116695396_20305577),ogm[GRCh37] 11q23.3q25(116682645_134939459)x3,ogm[GRCh37] 22q11.1q11.21(16695297_ 20356873)x3

3.5.2. In **Figure 20**, unbalanced translocations are indicated by magenta lines connecting the involved chromosomes and blue and/or red lines in the copy number track, associated with the magenta lines. In the genome browser, the translocation maps, with associated breakpoints and genes, can be visualized with the copy number gains and losses found in the copy number track. Copy number changes can also be visualized with the whole genome view.

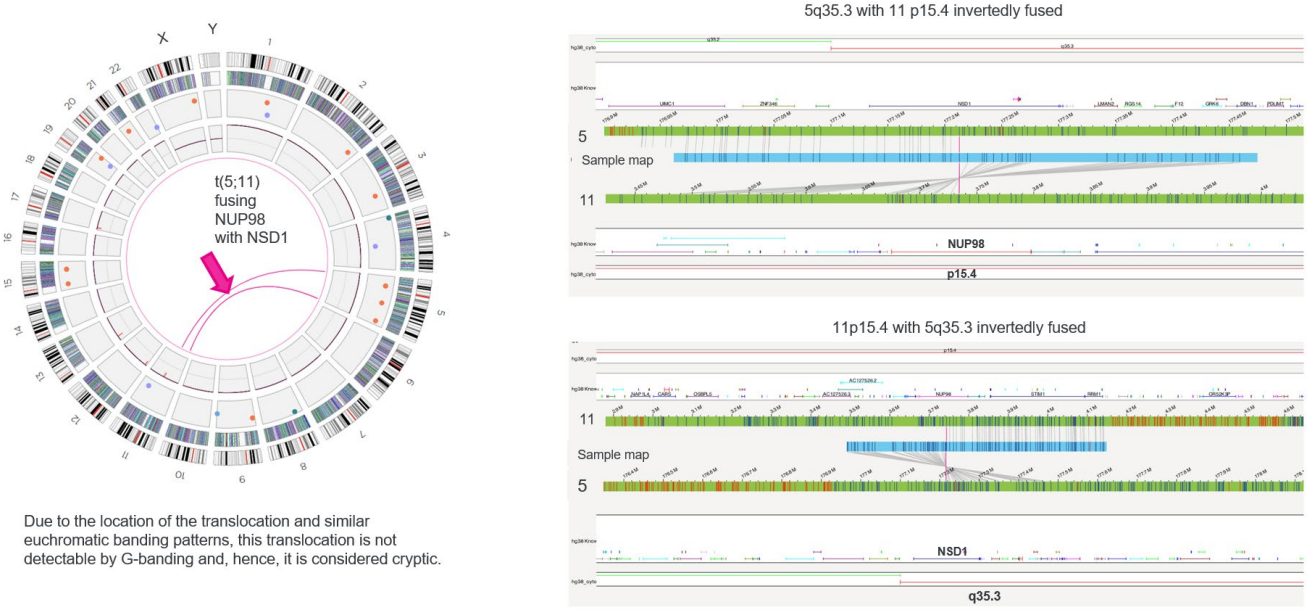


Figure 21: Cryptic translocation - ogm[GRCh38] – t(5;11)(q35.3;p15.4)(177212867_3734712)

3.5.3. Cryptic translocations, as seen in **Figure 21**, can be viewed as magenta lines in the Circos plot and translocation maps in the genome browser view. Translocations are considered cryptic because of their specific location in the chromosome, not detectable by other molecular genetic strategies .

3.6. Structural Variants: Inversions

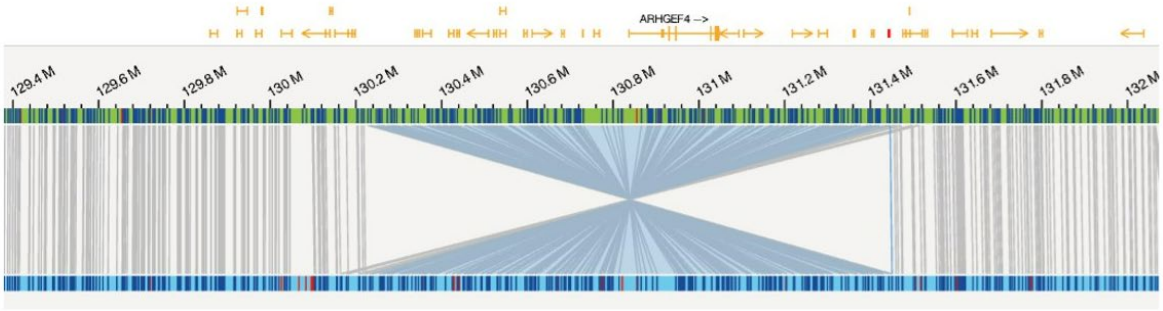


Figure 22: Simple inversion

3.6.1. Inversions are visualized in the genome browser at an inverted orientation of the sample map labels to the reference map labels. **Figure 22** displays inversions < 5 Mbp.

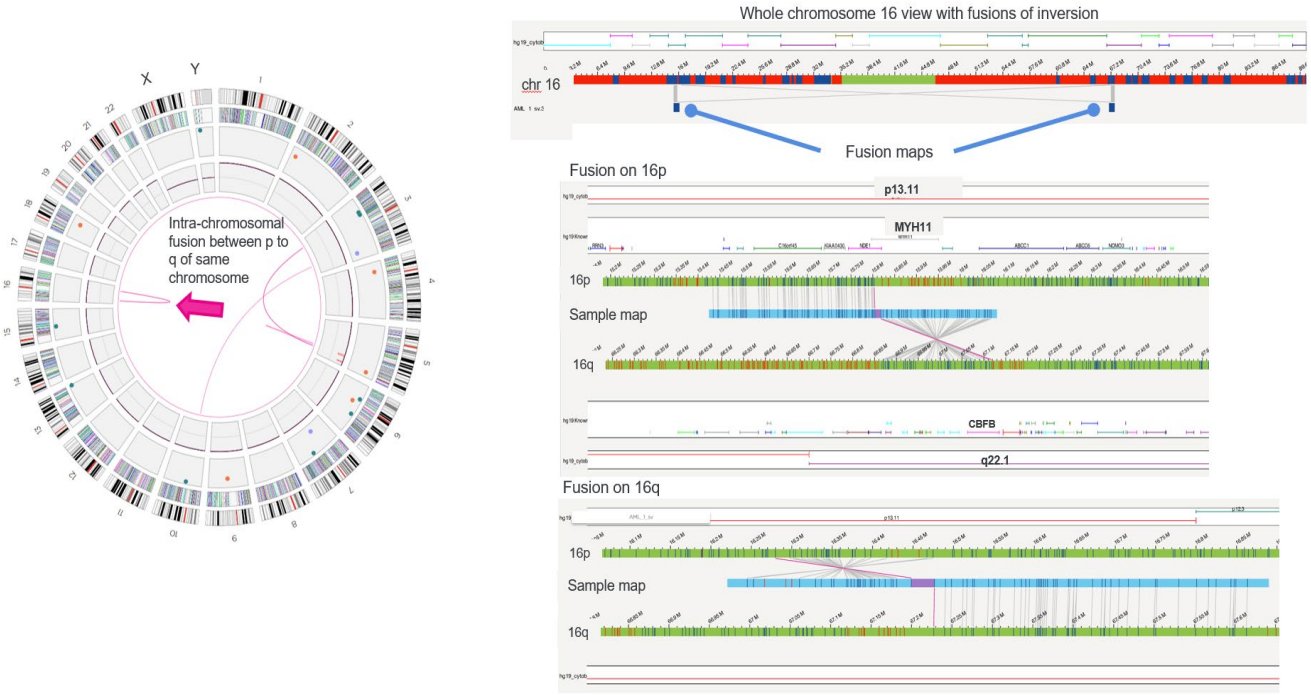


Figure 23: Pericentric inversion/fusion - ogm[GRCh37] inv(16)(p13.11q22.1)(15803116_67118000)

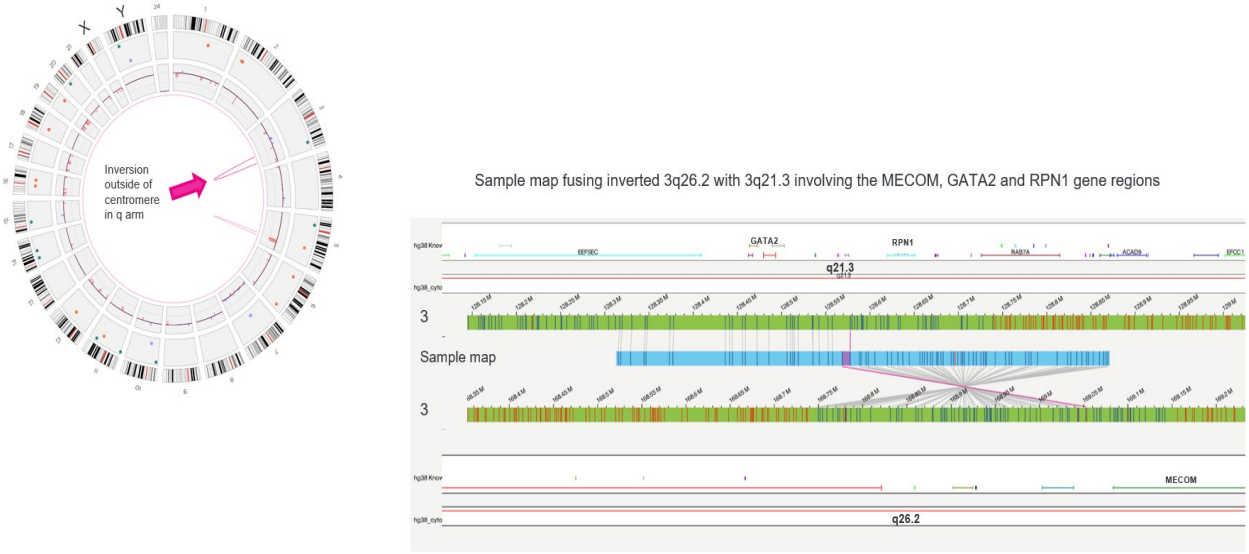


Figure 24: Paracentric inversion - ogm[GRCh38] inv(3q21.3q26.2)(128577641_169052490)

3.6.2. Large pericentric (see **Figure 23**) and paracentric (see **Figure 24**) inversions are indicated by magenta lines in the Circos plot. The sides of the inversions are captured by intra-chromosomal fusion maps that can be visualized in the genome browser.

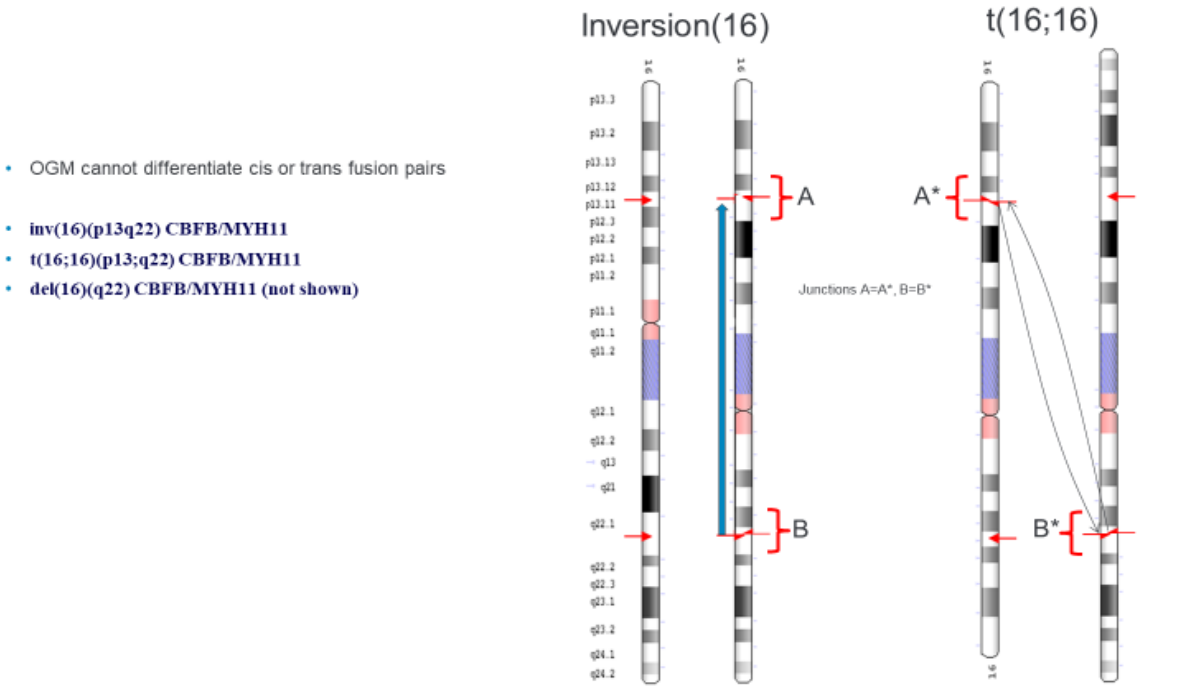


Figure 25: Inv(16) vs. t(16;16)

3.6.3. Optical genome mapping cannot differentiate between a translocation involving two homologs or an inversion happening at the same breakpoints (see **Figure 25**).

3.7. Absence of Heterozygosity (AOH) and Triploidy

3.7.1. Absence of heterozygosity (AOH) is a well-recognized genomic change by which heterozygous alleles are absent, rendering the sequence effectively homozygous. This homozygosity can result in human diseases including congenital and somatic disorders due to absence of wild-type alleles or biparental expression of an imprinted region. Triploidy is a chromosome abnormality that occurs when there is an extra set of chromosomes present in each cell. The signs and symptoms associated with triploidy vary but may include a variety of birth defects and unusually small size.

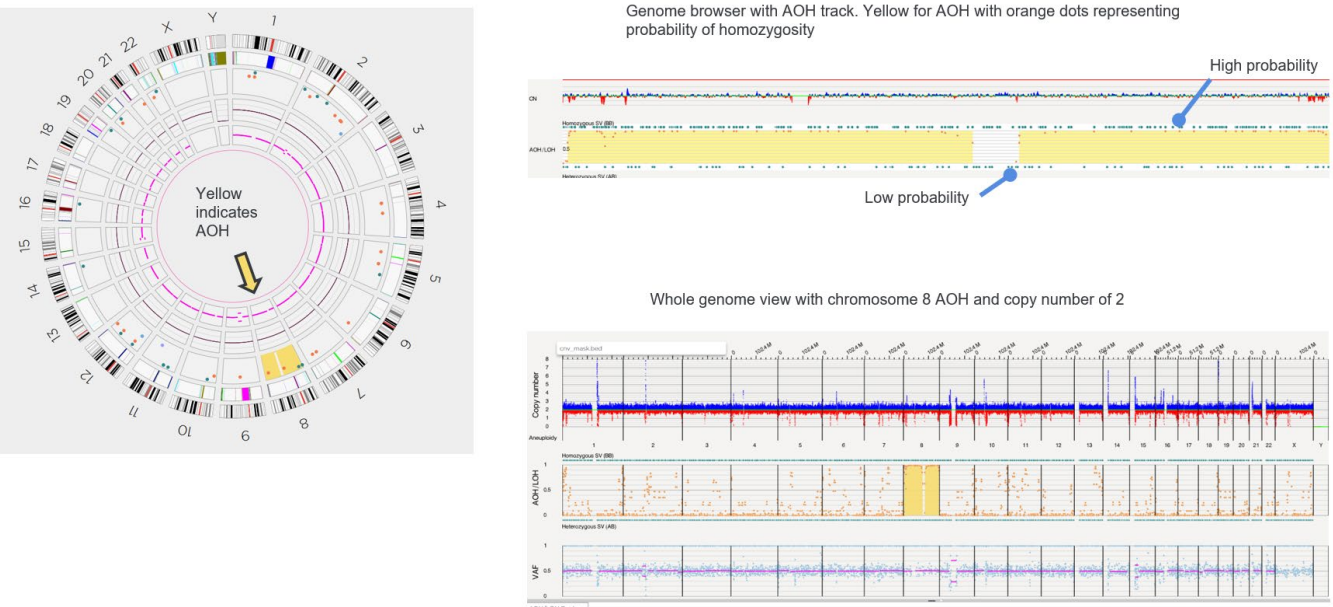


Figure 26: AOH: Chromosome 8

3.7.2. In **Figure 26**, a yellow region in the AOH track shows two identical homologs in chromosome 8, demonstrating absence of heterozygosity.

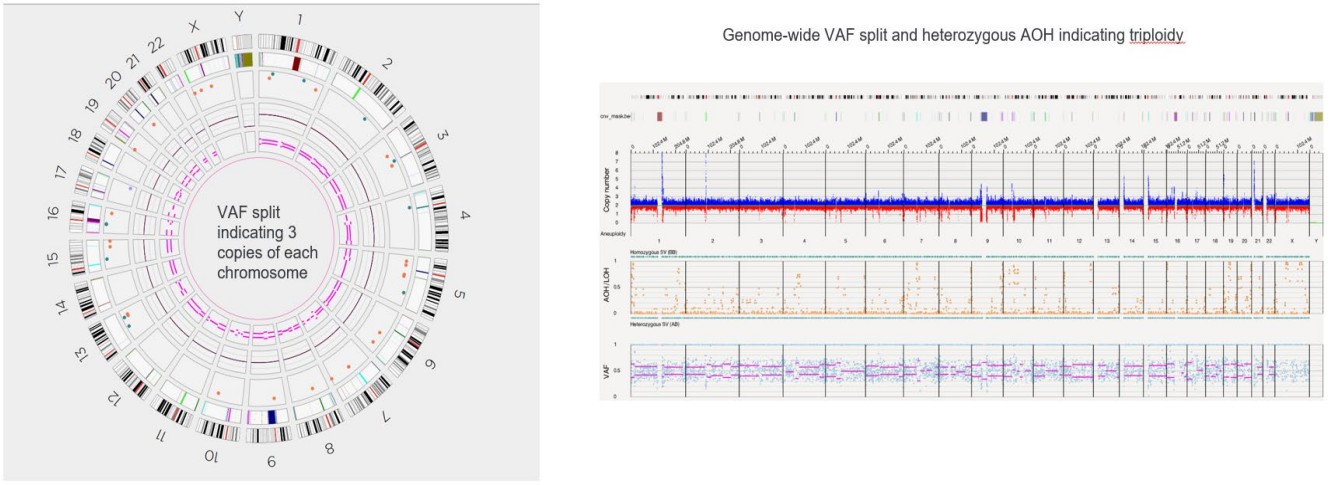


Figure 27: Polyploid - Triploidy

3.7.3. Triploidy– the magenta lines indicate that the variant allele frequency (VAF) is split in the Circos plot in **Figure 27** where there are three copies of each chromosome in this 69XXX sample. This represents the observation of three alleles across the genome in a triploidy case (i.e., 69XXX, 69XXY, 69XYY). In triploidy, for heterozygous loci, there are always two of one allele and one of another (three of the same allele where homozygous), resulting in 33% or 66% variant allele fraction. This is represented by

the pair of magenta lines around the inner ring. **Note:** a diploid sample will have only one magenta line.

3.8. Macrosatellite/Microsatellite of Repeat Expansions and Repeat Contractions

3.8.1. Bionano EnFocus pipelines are designed to characterize target loci. Currently, there are two EnFocus tools in the Bionano Access software suite: EnFocus Fragile X and EnFocus FSHD. In both pipelines, molecules aligning to the regions of interest are extracted and assembled. The resulting consensus maps can be used to characterize the repeats, which include repeat expansions (polymorphic nucleotide sequences scattered throughout the human genome) and repeat contractions (specific for the normal allele). Please refer to the *Fragile X* (P/N 30457) and *FSHD* (P/N 30321) *Theory of Operation Analysis* documents.

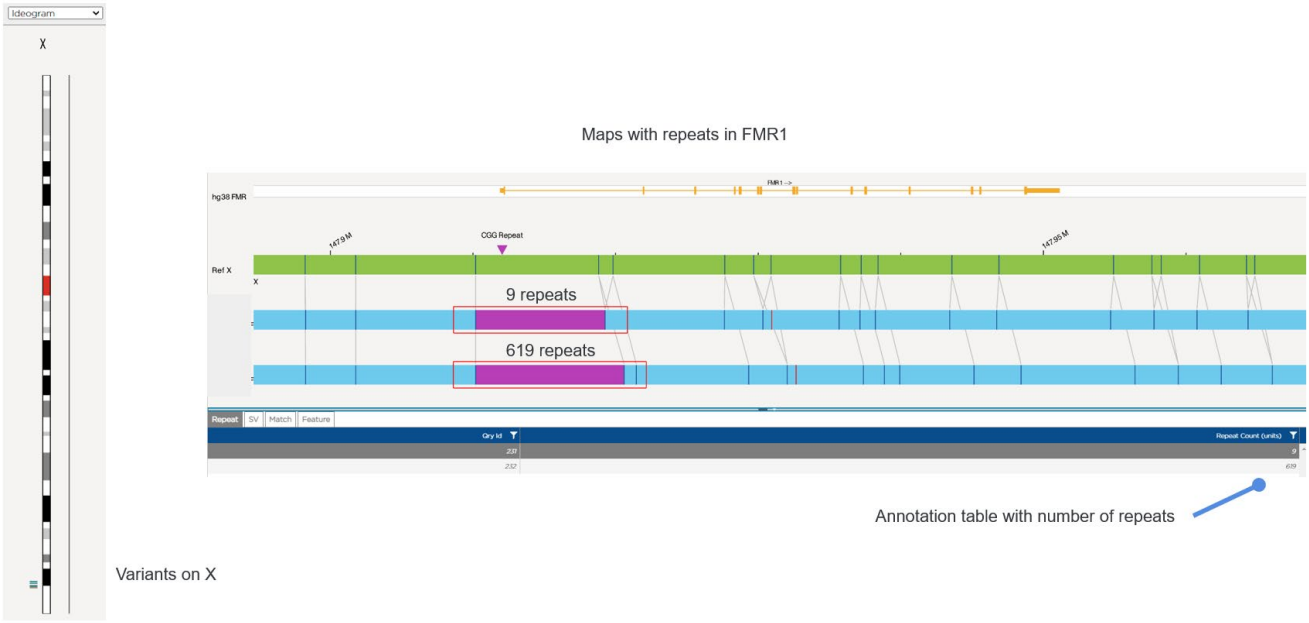


Figure 28: Fragile X – Repeat Expansion

3.8.2. Fragile X expansion information and maps can be visualized with the EnFocus Fragile X analysis tool, as seen in **Figure 28**. The gene structure of *FMR1* is shown in the top of the figure. The label intervals on the consensus maps that overlap the trinucleotide locus are colored in magenta. The number of repeats is computed by comparing the interval lengths on the maps and the interval lengths on the reference, subtracting a constant region (around the repeat expansion region), and converting to repeats (triplet repeat is three nucleotides per repeat unit). In this example, the repeat counts are 9 and 619. Please see the *Bionano Solve Theory of Operations: Structural Variant Calling* document (P/N 30110) for more detail.

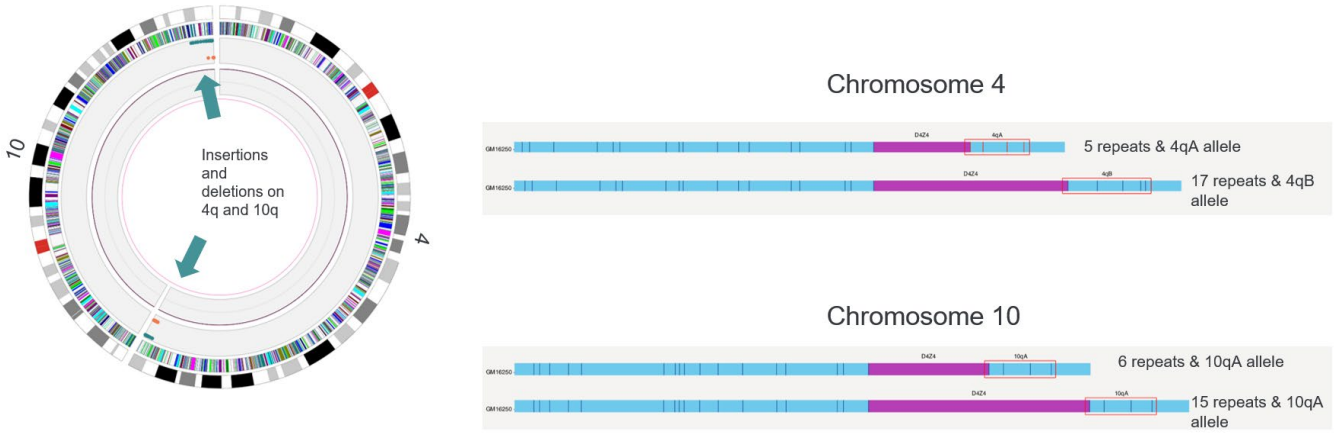


Figure 29: FSHD – Repeat contraction

3.8.3. Repeat contractions related to FSHD1 can be assessed with the EnFocus FSHD analysis tool. **Figure 29** depicts the two loci with D4Z4 macrosatellite repeats on 4q and 10q. The map regions that overlap the D4Z4 repeats on chromosomes 4 and 10 are colored in magenta. The lengths of the repeats are determined by comparing the interval lengths of the maps and the reference. The right most labels beyond the D4Z4 region are used to determine the A and B haplotypes.

3.9. Complex Variants

3.9.1. Complex variants are genomic rearrangements comprising multiple structural variants, typically involving three or more breakpoint junctions. Examples are isochromes and chromothripsis as these contribute to human genomic variation and can cause Mendelian disease.

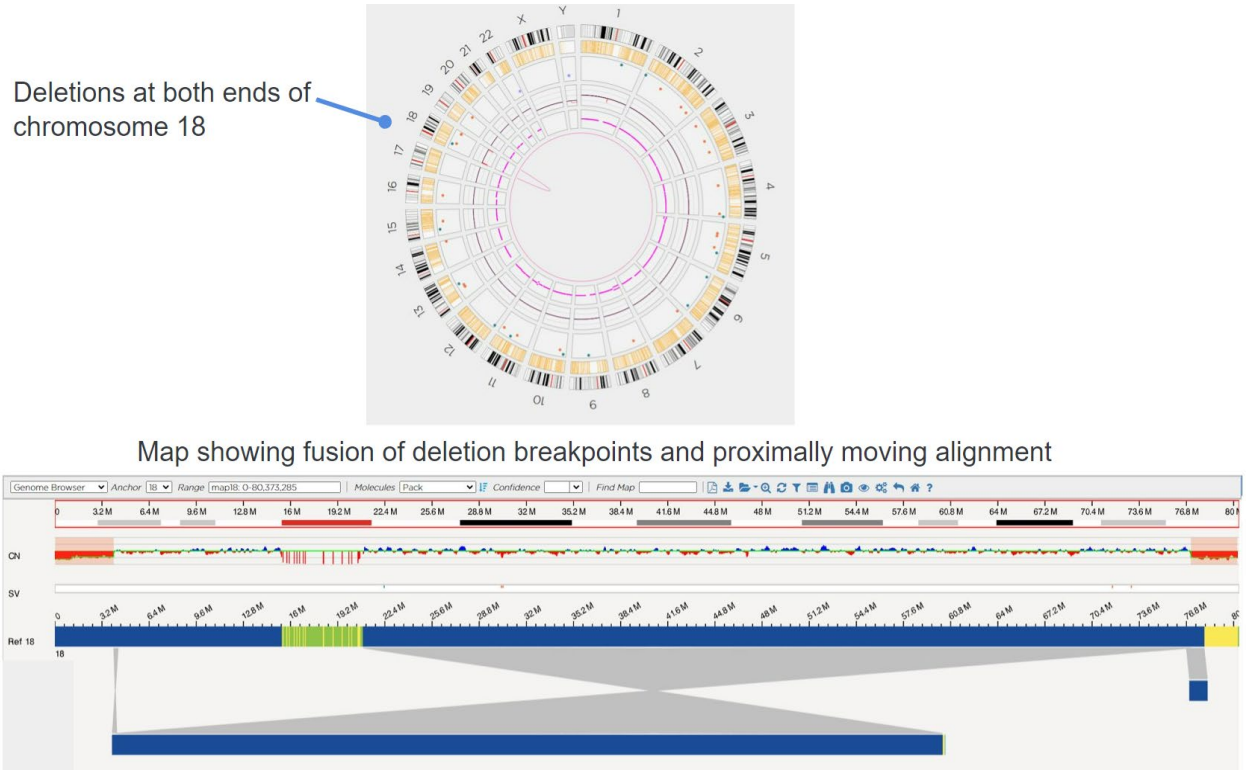


Figure 30: Ring chromosome

3.9.2. Ring chromosomes can be detected by OGM and are often indicated as shown in **Figure 30**. Here, a sub-telomeric fusion is displayed in the Circos plot by an intrachromosomal connection of the two ends of chromosome 18, and by CNV losses coordinated with the intrachromosomal fusion. In the genome browser, the copy number losses and the inverted fusion map are visualized.

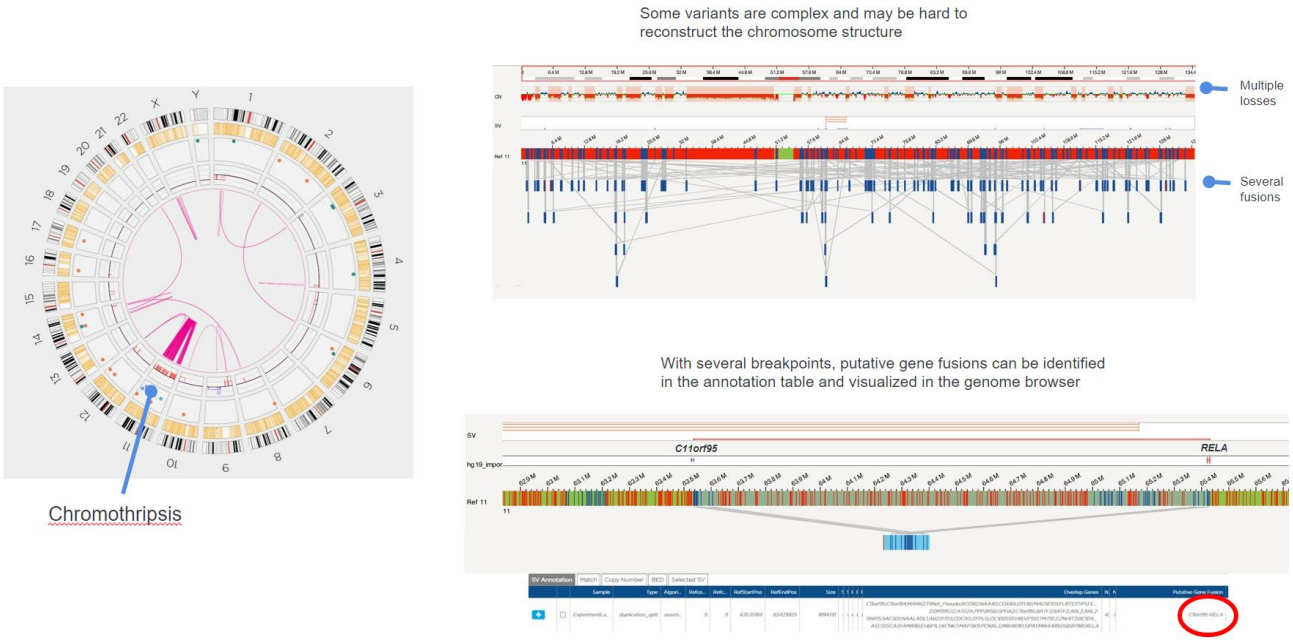


Figure 31: Complex rearrangements

3.9.3. In the Circos plot seen in **Figure 31**, chromothripsis (thripsis, in translation from Greek, means destruction into small parts) can be inferred by observation of many magenta translocation lines within a single chromosome and/or between a few chromosomes. In the genome browser, intrachromosomal fusion maps and/or interchromosomal translocation maps, and the putative gene fusions in the annotation tables, can provide additional information about the structure of chromothripsis.

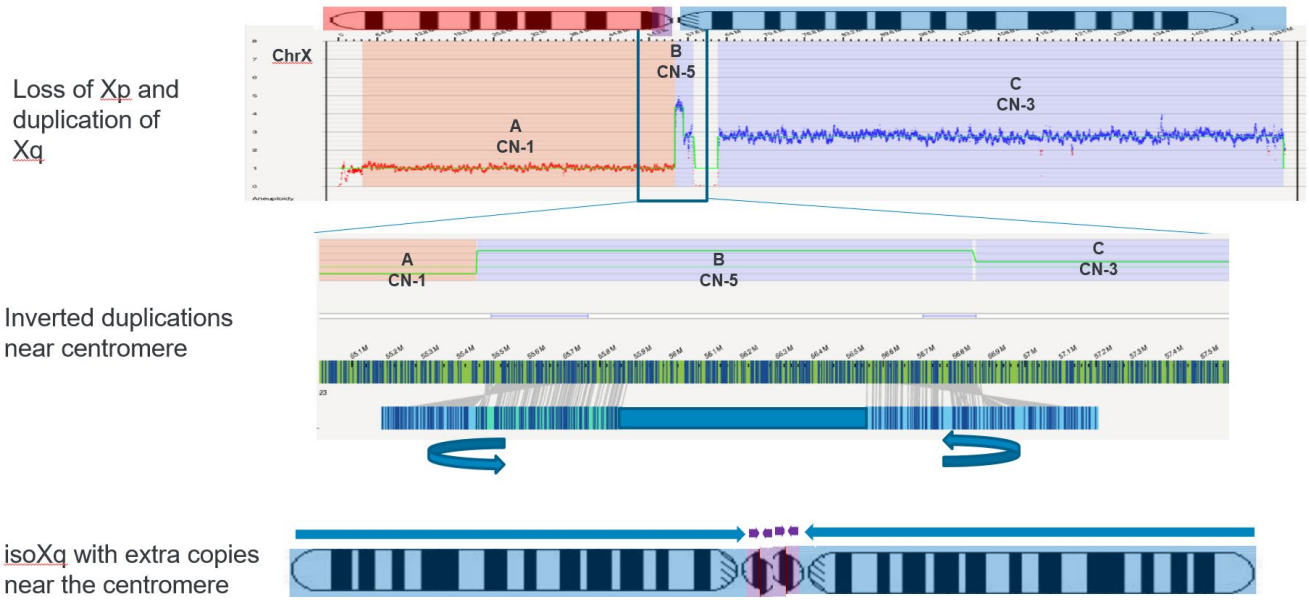
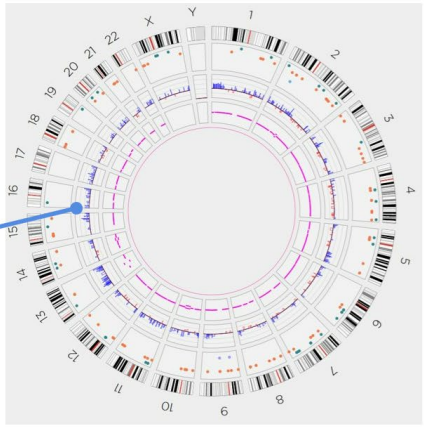


Figure 32: Complex X

3.9.4. Isochromosomes can be detected by gains and losses of whole chromosome arms within the same chromosome, as depicted in **Figure 32**.

4. INTERPRETING CONFLICTING VARIANT INFORMATION

Multiple small gains and losses in Circos plot and whole genome views indicate poor quality data. In addition, out-of-range quality control variation metrics warn of systematic bias.



Assembly CNV Statistic	Value
Percent above expected (2 Mbp window) *<20% acceptable*	43%
Percent above expected (6 Mbp window) *<20% acceptable*	80%

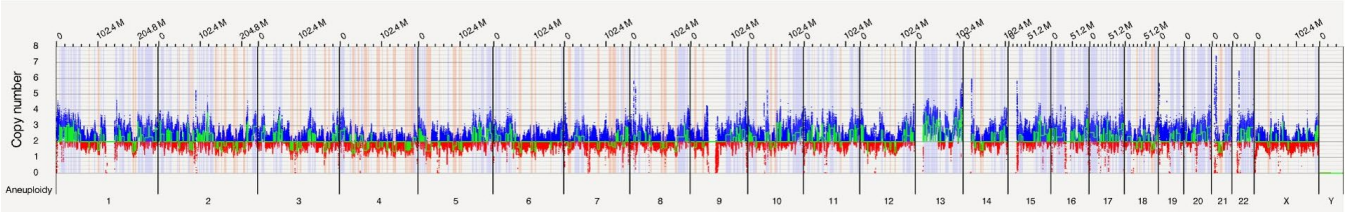


Figure 33: Noisy copy number data

4.1. In **Figure 33**, multiple small copy number changes are seen in the Circos plot and in the whole genome view, coupled with poor CNV statistics indicating noisy copy number data. Caution should be used when interpreting copy number changes. In **Figure 33**, it is impossible to distinguish true copy number change from background noise; therefore, the CNV data is unusable. CNV noise is usually due to ineffective removal of DNA-bound protein (DLE-1 or otherwise) from the DNA molecules, causing bias as to which molecules can travel into chip nanochannels. Using fresh, properly-stored Proteinase K usually solves the problem. Note that the quality of the SV is not affected by such noise in coverage depth.

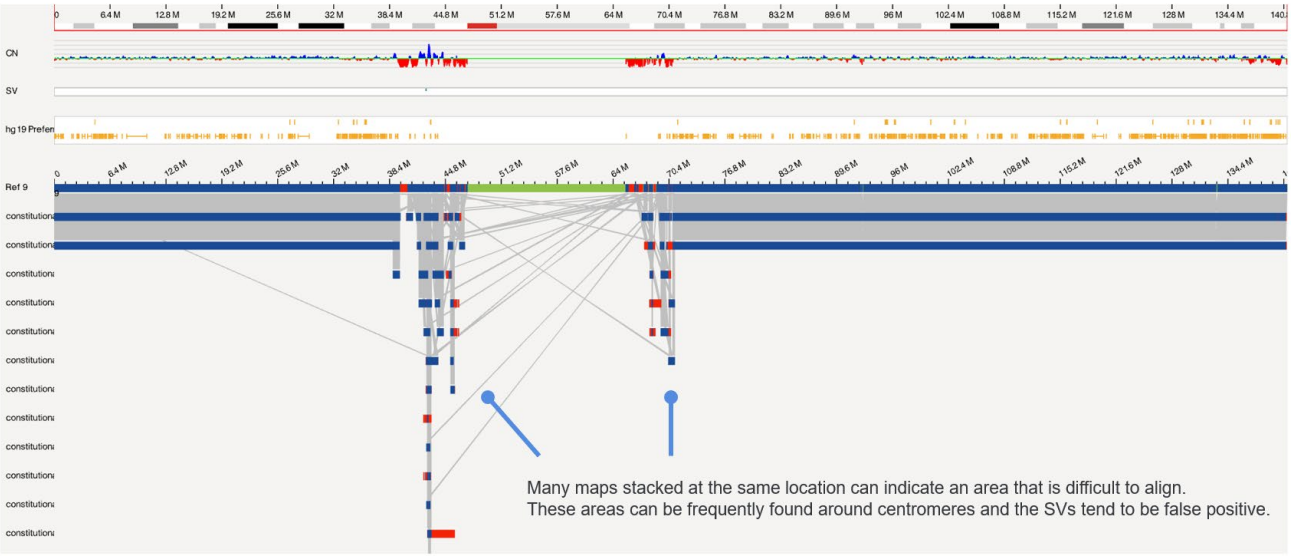


Figure 34: Stacks of maps

4.2. As seen in **Figure 34**, in the genome browser view, multiple stacked maps indicate the presence of large low copy repeats that have ambiguous and/or non-unique mapping, seen in repetitive areas of the genome and especially around centromeres. Caution should be used interpreting SVs in these areas.

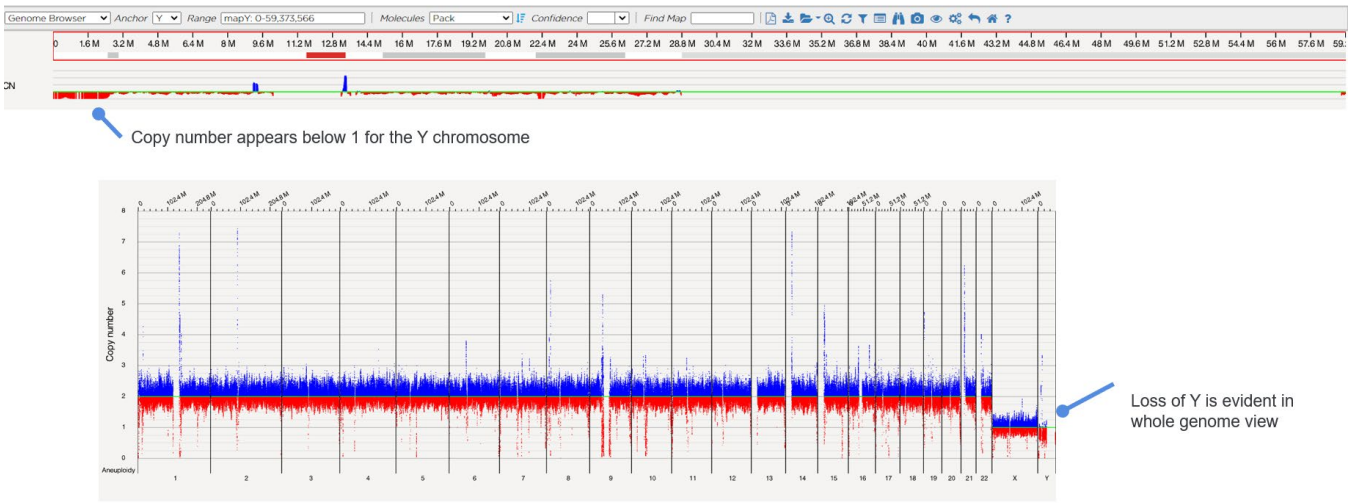


Figure 35: Masked variants – Y chromosome

4.3. The variability of coverage profile in chrY in control samples is substantially higher relative to other chromosomes. In fact, a sizable portion of the Y chromosome is masked due to high variance. Aneuploidy can still be called in such variable regions, but users will have to ignore the mask and use the confidence score as a guide to visually look for actual events. In **Figure 35**, the coverage of chrY is notably lower than the other chromosomes, and the confidence scores (scores of 1) pass the recommended threshold. The chrY loss is a true positive.

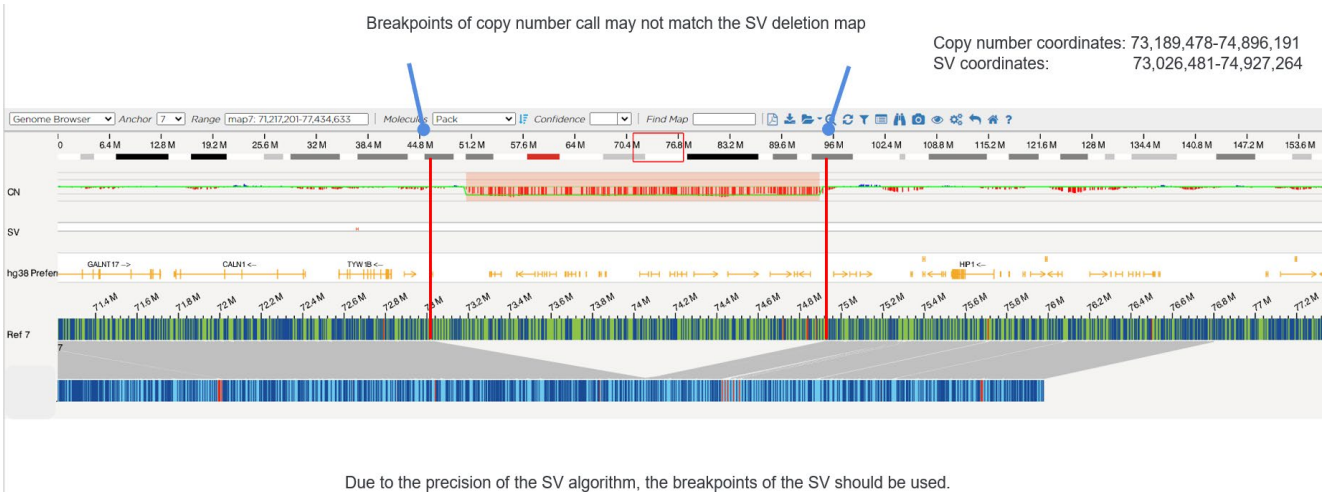


Figure 36: Differences between copy number tracks and SV map breakpoints

4.4. As indicated by the red bar in the copy number track and the deleted sample map in **Figure 36**, copy number changes >500 kbp should be picked up by both algorithms, except for terminal deletions and duplications. However, the two algorithms have called different breakpoints in this example. In general, the SV algorithm breakpoints are more precise and should take precedence over the CNV coordinates.

Figure 37: False positive copy number call

4.5. **Figure 37 A**. Here, a 933.1 kbp copy number gain (with a copy number of 2.470) has been detected in a constitutional/non-cancer sample. However, this example is likely to be a false positive. First, this is a constitutional sample, and a non-whole number copy number gain (i.e., 2.47 rather than 3) is unexpected. Second, interstitial copy number variants >500 kbp should be detectable by both the

CN and SV algorithms. It is unlikely that the SV algorithm would miss a gain occurring at a cellular fraction of 47%. Finally, as seen in **Figure 37 B**, the coverage gain of the call is not notably higher than the rest of the chromosome.

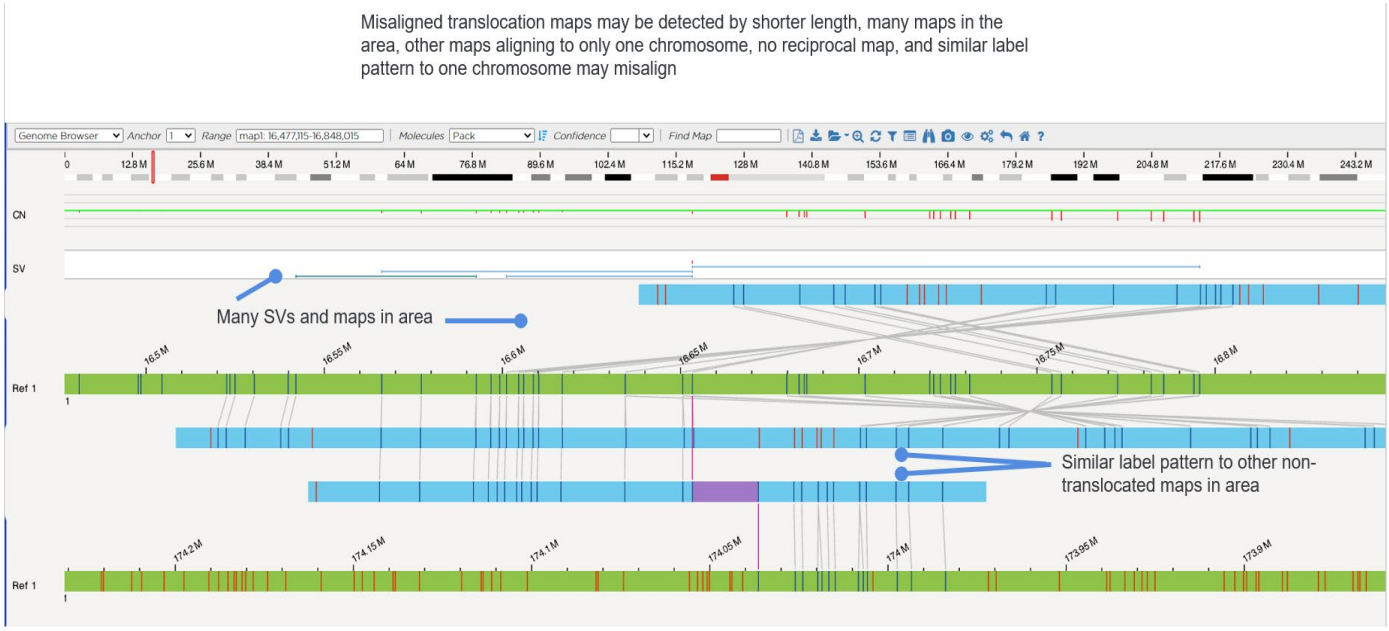


Figure 38: False positive translocations

4.6. In the genome browser view, translocation maps should be reviewed to determine validity. As seen in **Figure 38**, misaligned maps do occur. The map that called the translocation (or intra-chromosomal fusion) is a short map, and the alignment to 174 Mbp of Chr1 consists of only a few labels. Furthermore, that label pattern is mostly identical to the longer map just above, which called an inversion based on a much more robust alignment. Therefore, the translocation is likely a false positive due to a misalignment to 174 Mbp and the inversion is likely valid.

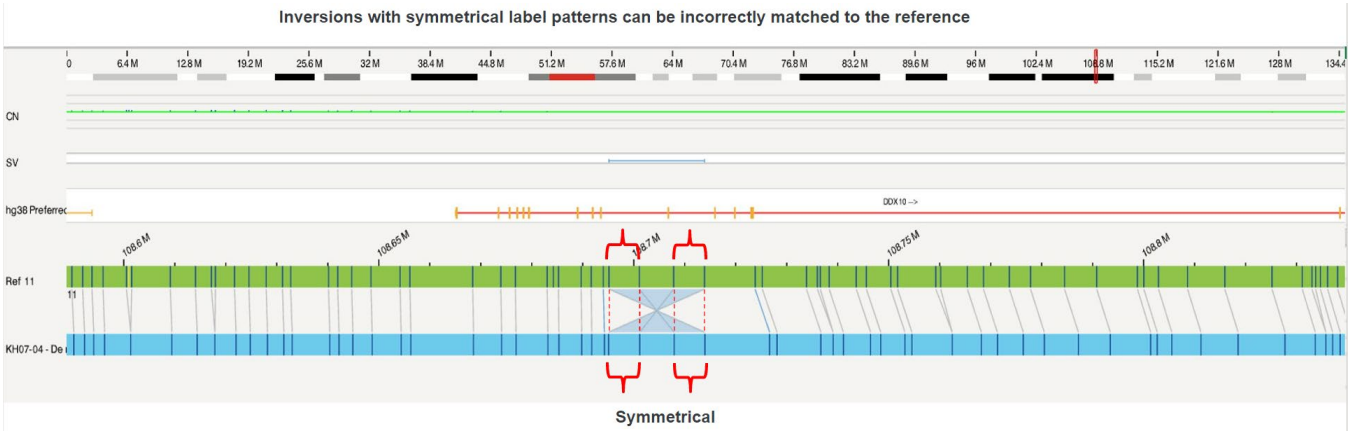


Figure 39: False positive inversions

4.7. In the genome browser view, the pattern for inversion maps should be reviewed for validity, as incorrect matching is seen in **Figure 39**. Care needs to be taken when there is a perfectly

symmetrical label pattern in inversions. Here, the inverted alignment could have been aligned vertically with the reference, resulting in a simple insertion event without the inversion.

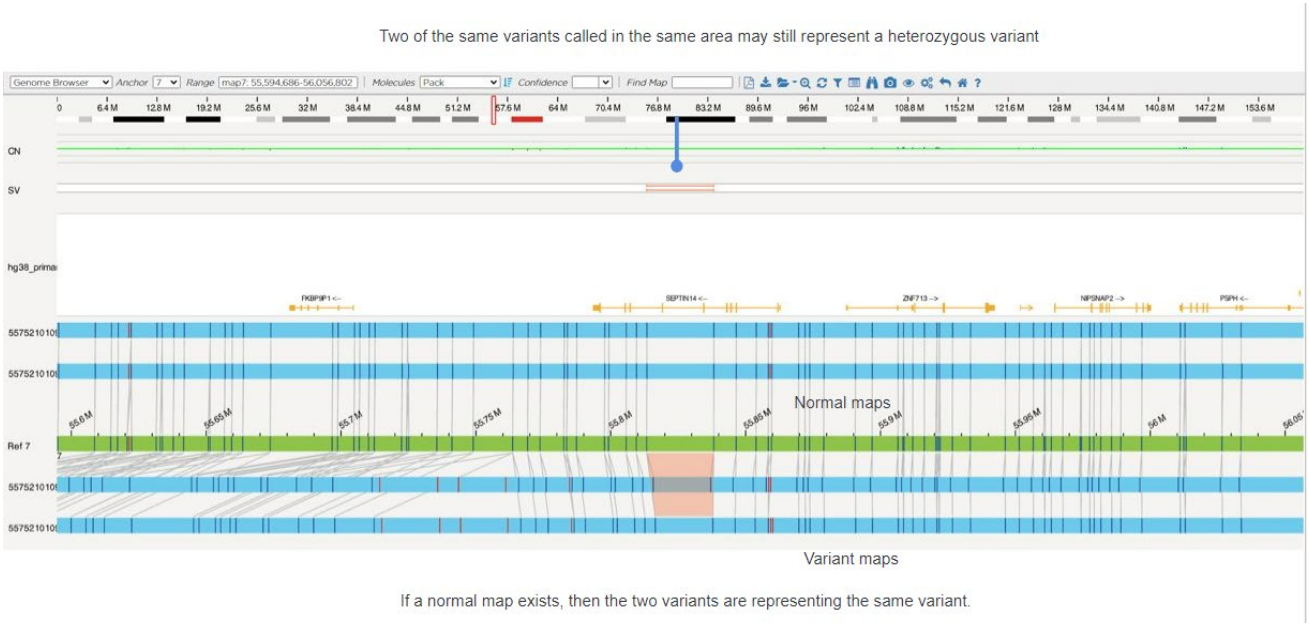


Figure 40: Homozygous variant is heterozygous

4.8. To rule out redundant maps indicating homozygosity, view all maps for the region in the genome browser view. **Figure 40** illustrates this point, where two deletions are called by the two variant maps in the bottom. However, the deletion is heterozygous because there is a reference allele captured by two normal maps. Due to over-splitting (in both the De Novo Assembly and the Rare Variant pipelines), redundant maps representing the same allele may be produced. Therefore, two of the same variants called in the same area may still represent a heterozygous variant. Refer to the zygosity or variant allele fraction value to infer zygosity.

Technical Assistance

For technical assistance, contact Bionano Genomics Technical Support.

You can retrieve documentation on Bionano products, SDS's, certificates of analysis, frequently asked questions, and other related documents from the Support website or by request through e-mail and telephone.

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