Comparison of Bionano optical genome mapping with conventional cytogenetic tests

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Introduction

Structural variant detection still relies mainly on traditional cytogenetic methods such as conventional chromosome analysis, Fluorescence *in situ* Hybridization or microarrays. Due to technical limitations, none of these methods alone is sufficient to solve most complex diagnostic cases.
Bionano optical genomic mapping (OGM) provides whole genome structural variation detection starting at 500 bp up to entire chromosomes and could potentially overcome the barriers that limit to date routine diagnostic methods. Here, we present the data from our validation study comparing Bionano optical mapping with cytogenetic standard of care tests.

Material and Methods

We selected 14 blood samples and two prenatal samples with either known (balanced and unbalanced) structural variants or copy number variants. Ultra high molecular weight DNA were extracted and labeled at specific sequence motifs. Molecules were then linearized in nanochannel arrays on specific Chips and imaged by the Saphyr Genome Imaging instrument. *De novo* genome assemblies were created and structural variants and CNVs were called by comparing sample maps to a reference.

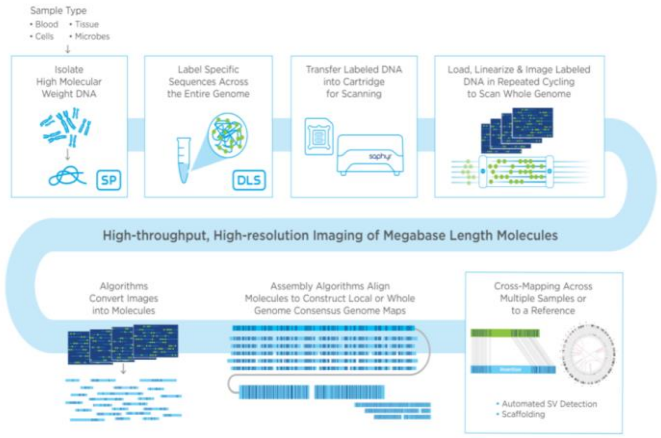

Figure 1: optical genomic mapping workflow (*https://bionanogenomics.com/clinical/cytogenomics/*)

Results

Table 1: Validation results. All known variants from chromosome analysis (including one aneuploidy, translocations, and an inversion) were detected by OGM. All deletions from microarray analysis were confirmed by OGM. However, only in 5 of 6 samples, known duplications from Array-CGH were called by OGM.

Variant class	Results from chromosome analysis or microarray	Results Optical genomic mapping
Aneuploidy	47,XY,+21	✓
Structural variants detected by conventional chromosome analysis	46,XX,t(4;8)(q31.3;p23.3)	✓
	46, XX, t(2;7)(p23;q11.2)	✓
	45,XY,der(4)t(4;13)(p15.2;q12),-13	✓
	46,XY,t(1;16)(p36.2;p12)	✓
	46,XY,inv(19)(p13.3q13.1)	✓
	46,XX.ish(HIRAx1,SHANK3x2)	✓
Copy number variants detected by microarray	arr[GRCh37] 2p16.3(49231108_49316968)x1	✓
	arr[GRCh37] 12q21.33q22(90941526_92699266)x1	✓
	arr[GRCh37] 1q21.1q21.2(146500972_147828089)x3, 15q11.2(22765628_23087554)x1	✓
	arr[GRCh37] 15q25.3(85829254_86088060)x3,15q26.1(90840773_91020940)x3	✓
	arr[GRCh37] 19p13.3(585113_1211699)x3	✗
	arr[GRCh37] 22q12.2(29712745_30184637)x3	✓
	arr[GRCh37] 20p13p12.3(4980093_5683443)x3	✓
	arr[GRCh37] 4q13.2(67934903_68058665)x3,4q13.2(68286752_68913048)x3	✓

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Representative cases

SAMPLE 1

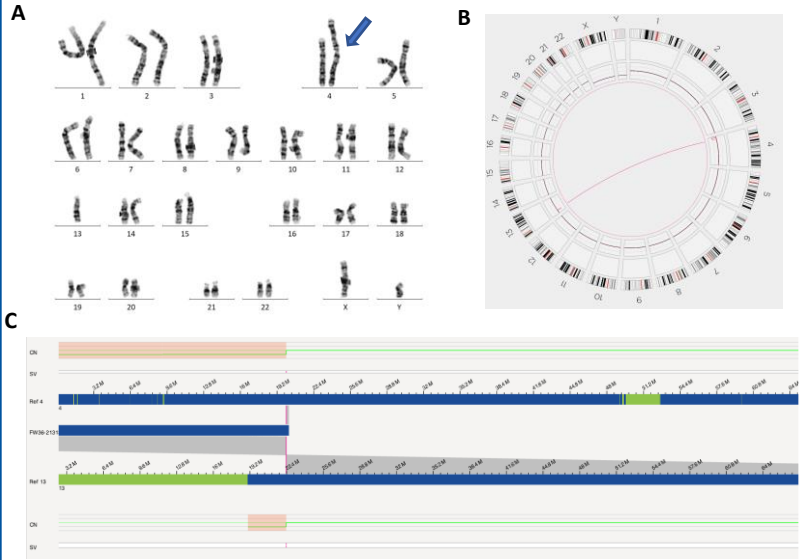

Figure 2: (A) Karyogram showing an unbalanced translocation between chromosomes 4 and 13 (45,XY,der(4)t(4;13)(p15.2;q12),-13) indicated by a blue arrow. (B) Circos plot view of the data confirming the unbalanced translocation between chromosomes 4 and 13 resulting in partial monosomy 4 and 13. (C) genome browser view of the unbalanced translocation with associated CN losses marked in orange.

SAMPLE 2

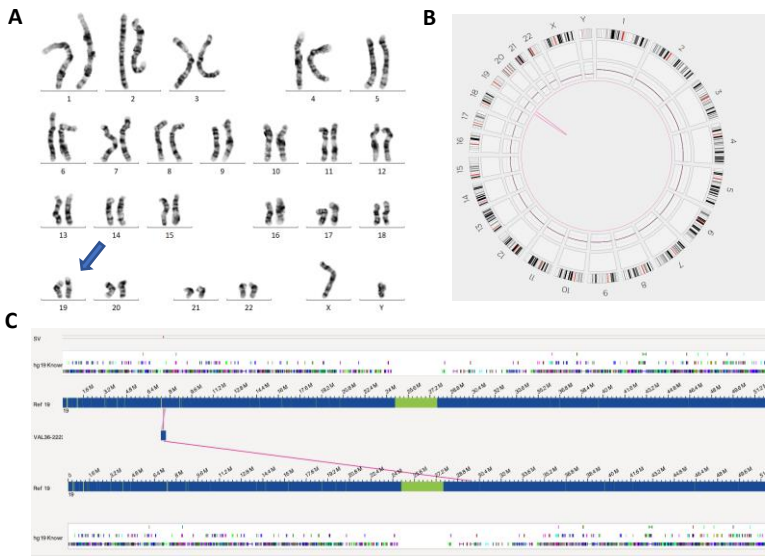

Figure 3: (A) Karyogram showing a pericentric inversion on chromosome 19 (46,XY,inv(19)(p13.3q13.1)) indicated by a blue arrow. (B) Circos plot view of the data confirming inv(19). (C) genome browser view with sample map mapping to p arm and q arm of chromosome 19. Break points were corrected (inv(19)(p13.2q12)) with specification down to gene level compared to chromosome analysis.

SAMPLE 3

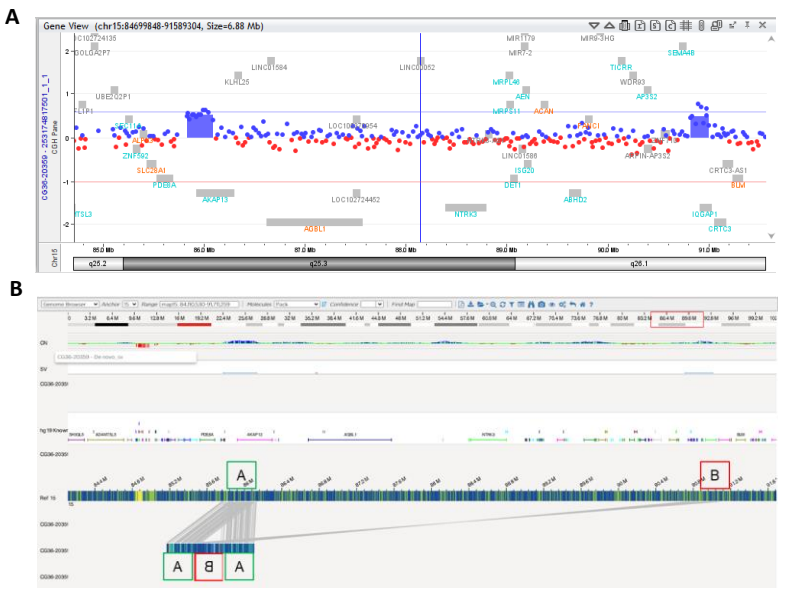

Figure 4: (A) CNV microarray data showing two gains on Chromosome 15 (B) whole genome browser view of the data confirming two gains but showing a complex structural aberration with an inverted insertion of one segment in the other.

Conclusion

Our results show that optical genomic mapping detected all structural variants previously known from chromosome analysis and almost all CNVs seen in microarray analysis. The higher resolution of optical mapping technology compared to chromosome analysis and microarray even allowed further specification of breakpoints down to gene level and revealed complex aberrations in some cases. Our results show that OGM can combine multiple routinely used diagnostic tests in one workflow potentially replacing them in the future.

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