Genome-wide Detection of All Structural Variants

Advances in sequencing technologies have barely changed the way structural variants are detected. NGS relies on short-read sequences that are mapped to a reference human genome and fails to identify most large insertions, deletions, and copy-number variations in the two-thirds of the genome that is repetitive. In addition, NGS does not reliably detect balanced SVs such as inversions and translocations.

Optical Genome Mapping (OGM) directly visualizes patterns of labels on intact DNA molecules to detect structural variation.

OGM accurately detects all classes of structural variants, which include balanced translocations, inversions, complex rearrangements, deletions, gains, insertions, and repeat expansions and contractions. All classes of structural variants are detected at high sensitivities.

Unlike sequencing-based methods, which are typically unable to detect insertions or identify where the extra sequence is inserted, OGM detects both deletions and insertions starting at 500 bp with high sensitivity. It detects mosaic variants down to as little as 5% variant allele fraction because it uses single-molecule analysis.

Ultra-high molecular weight DNA is isolated from blood, cells, tissue or tumor biopsies, and a single enzymatic reaction places 500,000 fluorescent labels all throughout the genome at a specific sequence motif. The labeled DNA molecules are linearized in nanochannel arrays on the Saphyr chip and imaged in an automated manner. Changes in the patterning or spacing of the labels are detected automatically, genome-wide, to call all structural variants.

OGM by the Numbers

Up to 99% — SV detection sensitivity

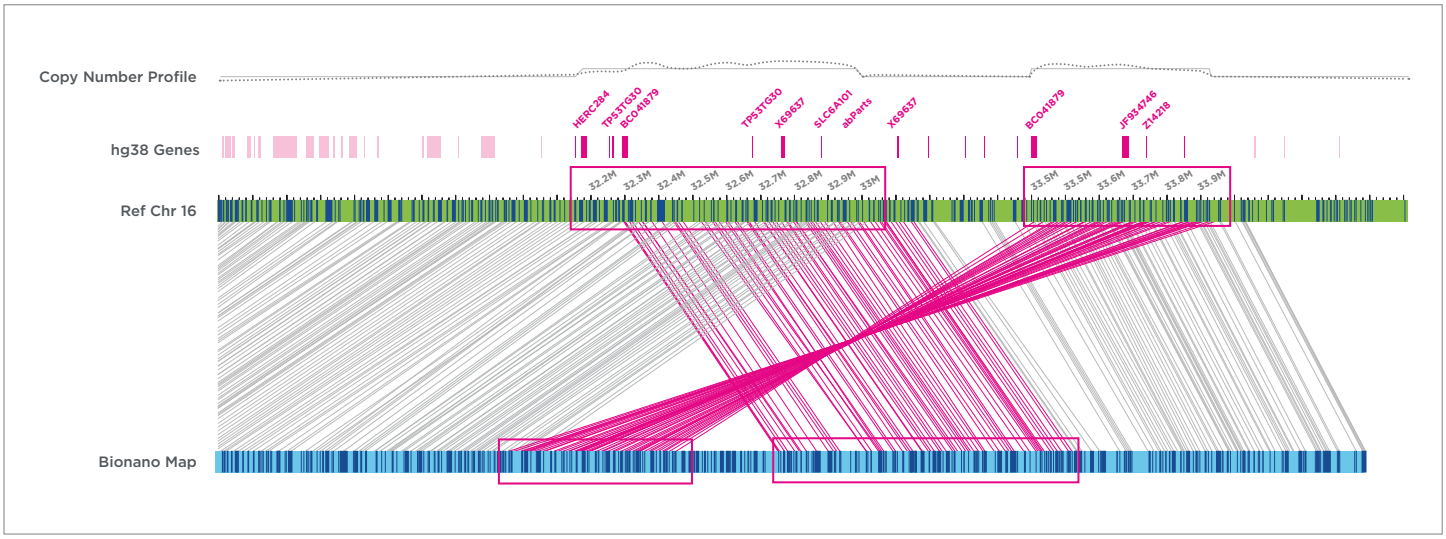
500 bp — Lower limit of resolution for detection of deletions and insertions

3-4 days — Turnaround time

10,000X — Resolution compared to karyotype

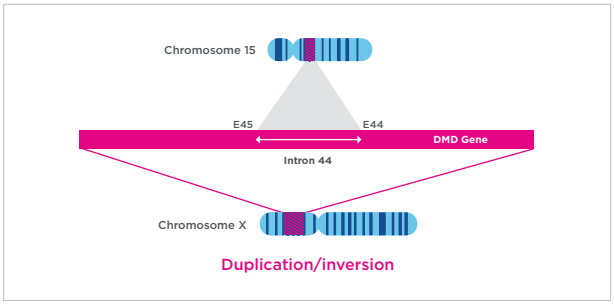
OGM Finds New Candidate Genes

In a newborn with Congenital Diaphragmatic Hernia (CDH), a severe developmental disorder affecting the diaphragm, lungs and sometimes heart, OGM detected two adjacent duplications, one direct and one inverted. OGM revealed a much more complex architecture than could be inferred from microarray data, and identified several additional candidate genes for CDH.[1]



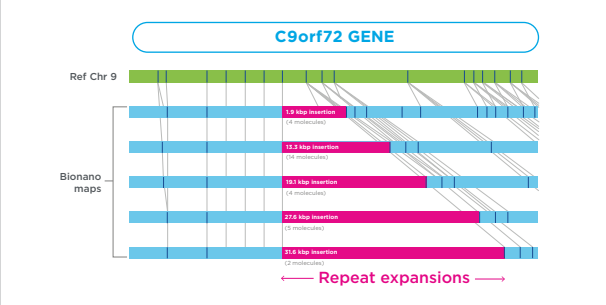
OGM Identifies New Variants in Known Genes

In a subject with Duchenne Muscular Dystrophy (DMD), a 420 kbp segment from chromosome 15 was duplicated in an inverted orientation in intron 44 of the Dystrophin gene. This insertion was not detected by NGS, and while chromosomal microarray can detect the duplication, its location and, therefore, implication in DMD could not be determined.[2]



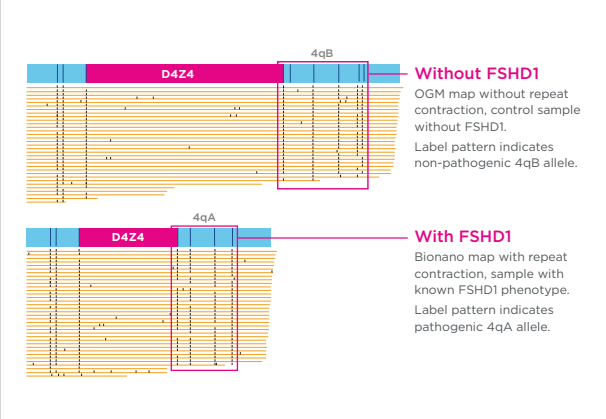
OGM Reveals Repeat Expansions

In a single postmortem brain sample from an ALS subject, OGM detected a highly mosaic range of expansions of the *C9orf72* GGGGCC repeat, ranging from the reference allele (not shown) to a 32 kbp expansion. No modern technology has been capable of spanning and measuring these large *C9orf72* repeat expansions.[3]



OGM Detects FSHD1

Facioscapulohumeral Muscular Dystrophy (FSHD1) is a common form of muscular dystrophy with an extremely complex genotype. Correct genotyping requires the accurate sizing of a very large repeat region in the subtelomeric region of chromosome 4, a correct determining of the pathogenic vs non-pathogenic allele, and the distinction between the chromosome 4 repeat and an almost identical repeat on chromosome 10 not related to the disease. A team from the University of Iowa published the largest clinical research study to date evaluating OGM for FSHD1. The study, published in the Journal of Molecular Diagnostics, concluded that OGM can be performed more quickly, accurately, and reproducibly than the current gold standard method of Southern blot analysis.[4]



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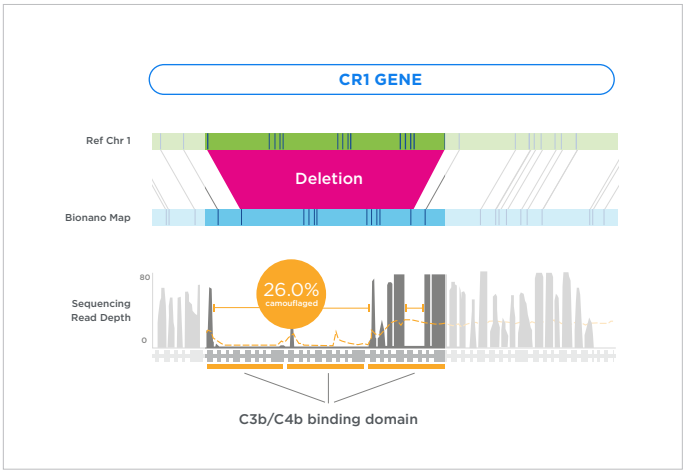
OGM Finds Variants Other Technologies Can't See

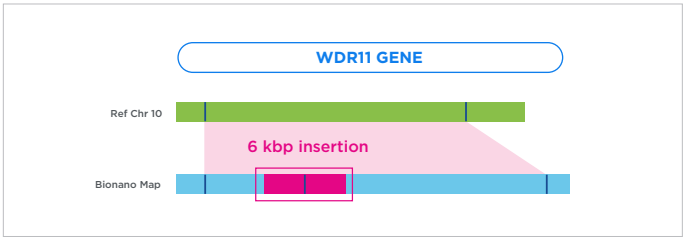
Because they're camouflaged:

Many protein-coding exons are 'camouflaged' in NGS datasets because of variably repeated binding domains—the exons occur in more than one gene or in tandem within the same gene, making correct alignment of short reads impossible. OGM allowed for the direct measurement of the number of C3b/C4b binding domains for each haplotype in *CR1*, an Alzheimer-associated gene, in this subject with Alzheimer's Disease.[3]



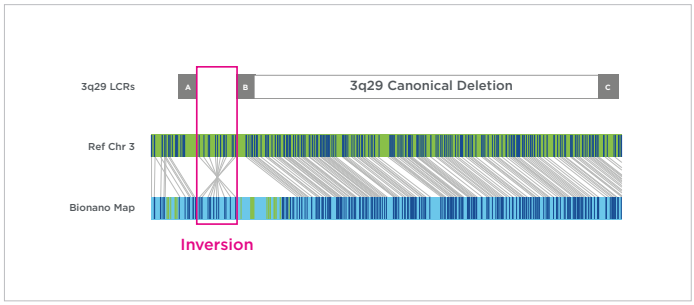
Because they're insertions:

While deletions are somewhat easier to detect by NGS, insertions are rarely picked up from NGS data. In a genetic male subject with gonadal dysgenesis, OGM identified a 6 kbp insertion in the *WDR11* gene, associated with abnormal testes development and cryptorchidism.[2]



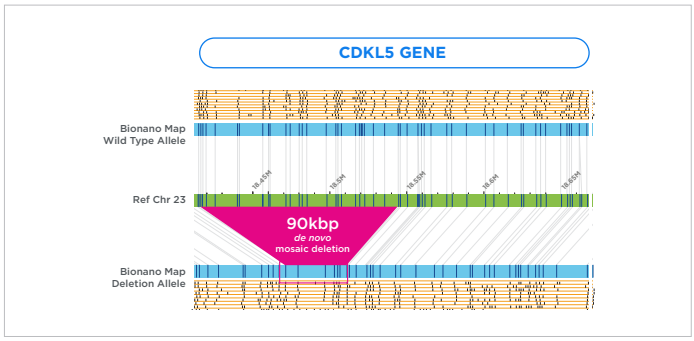
Because they're flanked by segmental duplications or are in other complex regions of the genome:

3q29 Microdeletion syndrome is present when a 1.5 Mbp region between two segmental duplications (also called Low Copy Repeats (LCR)) is deleted. It is thought that inversions in the parents between LCRs in this region predispose to the deletion in the child. Here, OGM detected a 350 kbp inversion between LCR A and B, something that's not been possible with any other genome analysis technology.[5]



Because they're mosaic:

A juvenile subject with epilepsy, hypotonia and developmental delay, extensively studied as part of the Undiagnosed Disease Network, remained undiagnosed. OGM found a 90 kbp mosaic deletion in *CDKL5*, an X-linked gene essential for normal brain development and function, and a phenotype that perfectly matches the subject's. The wild type allele is shown on top, and the deletion allele below.[2]

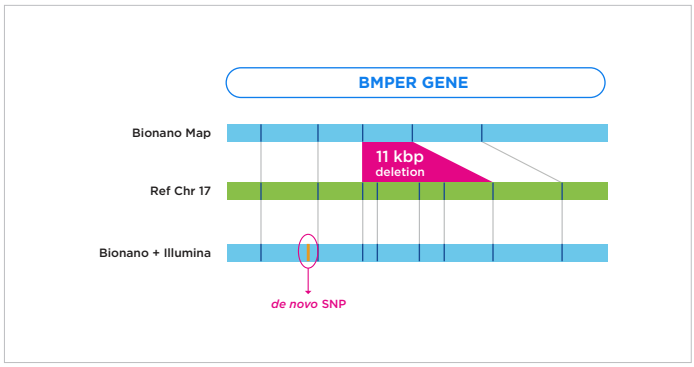


OGM Can be Combined with NGS

To find compound heterozygous variants:

In a subject with a complex phenotype and a variety of growth and developmental defects, OGM detected an 11 kbp deletion in the *BMPER* gene inherited from the mother, while a *de novo* SNP in the same gene was detected on the other allele. This combination creates a compound heterozygous mutation, only detected by a combination of NGS and OGM.[2]

BMPER is an autosomal recessive gene that regulates the Bone Morphogenetic Protein (BMP) and the phenotype matched a potential *BMPER* disruption.



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3 Ways to Get Bionano Data

Get the Service

Bionano Data Services

Submit your samples to Bionano Data Services and receive an appropriately filtered set of structural variant calls. SV data is presented using the Bionano Access® visualization software. Files can be exported in the format of your choice.

The Bionano Support team will work with you on experiment design and analysis training. Full analysis is available as an option.

Sample Types Accepted – Frozen, Mammalian Preferred

- Tissue Biopsies
- Blood
- Cultured Cells
- Bone Marrow Aspirates

Pricing available upon request.

- Diploid/Genetic disease samples collected at 120x
- Mosaic/Cancer samples collected at 400x
- Low-frequency variant samples collected up to 1600x

Get the Consumables

Reagent Rental Agreement

Run samples in-house with a Saphyr® Instrument free of charge for the duration of your project. The Bionano Support team will install the Saphyr System and provide training on sample preparation, instrument operation, and data analysis.

Please contact Bionano to request a reagent rental quote.

- Pricing is based on total genome commitment during a 6-month period
- Per-genome pricing includes DNA isolation, labeling, chips, and Bionano Compute On Demand
- Installation and training included

Get the Saphyr® System

System AND Consumables Purchase

Purchase the Saphyr System for your institution without any reagent commitment. The Bionano Support team will install the Saphyr System and provide training on sample preparation, instrument operation, and data analysis.

Saphyr System Components

- Saphyr Instrument
- Saphyr Chips
- Bionano Prep Kits
- Bionano Access Server
- Bionano Access Software
- Bionano Compute On Demand (optional)

Please contact Bionano for a detailed quote. Pricing may vary, depending on region, availability, and secondary hardware needs.

- Saphyr System includes installation and training
- Volume-based, per-genome consumable pricing
- Consumables include DNA isolation, labeling, chips, and Bionano Compute On Demand

To see all genetic disease case studies, presentations, and additional materials, visit bionano.com/geneticdiseases

1. High S. Advanced analysis of risk loci in congenital disorders using Bionano optical genome mapping. ASHG Bionano Symposium. 2019. https://bionanogenomics.com/videos/ashg-2019-series-dr-frances-high/ 2. Barseghyan H. Bionano mapping for evaluation of structural variants in genetic diseases. ASHG Bionano Symposium. 2019. https://bionanogenomics.com/videos/bionano-ashg-symposium-at-ashg-2019-hayk-barseghyan/ 3. Ebbert MTW. Resolving complex genomic haplotypes in neurodegenerative disorders using Bionano Genomics Saphyr System. ASHG Bionano Symposium. 2019. https://bionanogenomics.com/videos/ashg-2019-series-dr-mark-t-w-ebbert/ 4. Stence AA, Thomason JG, Pruessner JA, et al. Validation of Optical Genome Mapping for the Molecular Diagnosis of Facioscapulohumeral Muscular Dystrophy. J Mol Diagn. 2021;23(11):1506-1514. doi:10.1016/j.jmoldx.2021.07.021 5. Yilmaz F, Gurusamy U, Mosley TJ, et al. Multi-modal investigation of the schizophrenia-associated 3q29 genomic interval reveals global genetic diversity with unique haplotypes and segments that increase the risk for non-allelic homologous recombination. medRxiv 2021.11.10.21266197; doi: https://doi.org/10.1101/2021.11.10.21266197

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