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Optical Genome Mapping + Next-Gen Sequencing

Optical genome mapping (OGM) provides a unique complement to NGS across a wide variety of applications, with an unbiased, genome-wide evaluation of structural variants >500 bp in size. Although next-generation sequencing (NGS) provides reliable detection of single nucleotide variants and small indels, its ability to identify larger copy number and structural variants is significantly limited. Several research studies have combined OGM and NGS in the evaluation of cancer samples, and others have reported how OGM solved previously unsolved cases by identifying variants missed by short-read and long-read NGS.

ONCOLOGY APPLICATIONS

Publication	Summary of Key Points
High-resolution structural variant profiling of myelodysplastic syndromes by optical genome mapping uncovers cryptic aberrations of prognostic and therapeutic significance. Kanagal-Shamanna Lab MD Anderson Cancer Center *Leukemia*. 2022 Aug 1. doi: https://doi.org/10.1038/s41375-022-01652-8	• 101 consecutive MDS samples were evaluated with traditional cytogenetic methods (karyotyping, FISH, CMA), an 81-gene NGS panel, and OGM • OGM found nearly double the number of clinically relevant pathogenic variants compared to traditional cytogenetics • OGM findings could inform different prognostic risk classification or identify important additional variants in 28% of study participants • Changes to CCSS and IPSS-R risk scores in 21% and 17% of subjects, respectively. • Additional 13% of samples had additional alterations researchers suggest could be used for therapy selection/ response and disease monitoring • The combination of OGM and NGS resulted in the detection of at least one clinically significant abnormality in 97 of 101 samples
Structure, dynamics, and impact of replication stress-induced structural variants in hepatocellular carcinoma. Zucman-Rossi and Letouzé Labs Sorbonne Université *Cancer Res.* 2022 Apr 15;82(8):1470-1481. doi: https://doi.org/10.1158/0008-5472.CAN-21-3665	• Combined OGM and whole genome sequencing (WGS) to maximize the detection of pathogenic variants, and to investigate and resolve complex rearrangements • Of all SVs detected using OGM, only 63% were also detected by WGS • OGM revealed a median of 1.4 times more SVs than WGS, ranging from tandem duplications to complex genomic aberrations in the tumor cells

CG-0015_Rev. A_OGM+NGS_ Key Publications 01/27/23

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ONCOLOGY APPLICATIONS (CON'T)

Publication	Summary of Key Points
Clinical utility of combined optical genome mapping and 523-gene next generation sequencing panel for comprehensive evaluation of myeloid cancers. Kolhe Lab Augusta University Preprint: *medRxiv*. 2022 Jan 17. doi: https://doi.org/10.1101/2022.01.15.22269355	• Evaluated the use of OGM and a 523-gene NGS panel for genomic profiling of 15 myeloid tumors and compared results to karyotyping, FISH, and a 54-gene NGS panel • Results demonstrated 100% analytical concordance of OGM and the 523-gene NGS panel for variants found with traditional methods • In addition, OGM better characterized structural variants (SVs) previously reported by karyotyping in five samples and identified additional translocations and 11 CNVs • Demonstrated that combination of OGM and NGS is beneficial for comprehensive genomic profiling of myeloid neoplasm and NxClinical software enables simultaneous visualization and CNV confirmation
Genetic Disease Applications	
Application of full-genome analysis to diagnose rare monogenic disorders Shieh, Penon-Portmann, and Wong Labs University of California – San Francisco *PGenom Med*. 2021 Sept 23;6(77) doi: https://doi.org/10.1038/s41525-021-00241-5	• Describes a Full-Genome Analysis (FGA) approach using NGS linked-read sequencing and OGM to evaluate full spectrum of genetic variation in inherited genetic disorders • FGA was used in 50 subjects previously undiagnosed by either trio whole exome sequencing (23/50) and/or array (43/50) • FGA demonstrated an overall rate of detecting pathogenic variants of 40% (20/50) and identified candidate variants in 60% (18/30) of the remaining subjects. Lastly, FGA identified SVs and small variants in 8 of the 23 subjects missed by trio WES
16p13.11p11.2 triplication syndrome: a new recognizable genomic disorder characterized by optical genome mapping and whole genome sequencing Malan Lab Hôpital Necker-Enfants Malades *Eur J Hum Genet*. 2022 Apr;30:712-720. doi: https://doi.org/10.1038/s41431-022-01094-x	• Report of two unrelated subjects with a de novo 16p13.11p11.2 triplication associated with a 16p11.2 duplication, detected by CMA • Short-read WGS could not map any of the breakpoints • OGM determined the relative orientation of the triplicated and duplicated segments as well as the genomic positions of the breakpoints • Insights from OGM allowed authors to unravel the mechanism of these complex chromosomal rearrangements involving segmental duplications, propose a mechanism, and report a new clinically recognizable genomic disorder

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GENETIC DISEASE APPLICATIONS (CONT.)

Publication	Summary of Key Points
Optical genome mapping improves genetic diagnosis in chronic granulomatous diseases Xiaochuan Wang Lab Children's Hospital of Fudan University Preprint: *Research Square*. 2022 Feb 22. doi: https://doi.org/10.21203/rs.3.rs-1290086/v1	• Case series evaluating three subjects with suspicion of chronic granulomatous disease that were negative by NGS (panel and WES) • OGM was performed and identified a novel pathogenic ~1.5 kbp deletion in a causative gene in 1/3 subjects • Demonstrates ability to identify disease-causing variants missed by sequencing technologies
Marfan syndrome caused by disruption of the *FBN1* gene due to a reciprocal chromosome translocation Gläser Lab University of Freiburg *Genes*. 2021 Nov 21;12(11):1836. doi: https://doi.org/10.3390/genes12111836	• Case report of a family with suspicion of Marfan syndrome with no pathogenic variants identified on NGS analysis of *FBN1* gene, but with a reciprocal balanced translocation between chromosomes 2 and 15 • OGM was performed and mapped the breakpoint within the *FBN1* gene on chromosome 15—later confirmed by targeted sequencing—disrupting the gene and likely explaining the observed phenotype • First report of a reciprocal translocation in the *FBN1* gene associated with a typical Marfan syndrome presentation
Optical genome mapping identifies a germline retrotransposon insertion in *SMARCB1* in two siblings with atypical teratoid rhabdoid tumors Sabatella and Kuiper Labs Princess Maxima Centre for Pediatric Oncology Radboud University Medical Center *J Pathol*. 2021 Oct;255:202–211. doi: https://doi.org/10.1002/path.5755	• Case report of a family with two siblings born from healthy parents who were both neonatally diagnosed with atypical teratoid rhabdoid tumor (ATRT), associated with acquired homozygosity of *SMARCB1* • WES and WGS failed to identify germline or somatic *SMARCB1* pathogenic mutations • OGM detected an insertion of ~2.8 kb within intron 2 of *SMARCB1* • Further characterization with long-read sequencing identified this insertion to be a SINE-VNTR-Alu, subfamily E (SVA-E) retrotransposon element, which was present in a mosaic state in the mother.

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