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Optical Genome Mapping: Analysis for Constitutional Genetic Disorders

Optical genome mapping (OGM) has been evaluated for the analysis of structural variants (SVs) in constitutional genetic disorders in a growing number of studies. Several key studies compared OGM results to traditional methods of karyotyping, fluorescence in situ hybridization (FISH), and chromosomal microarray (CMA) with consistently high concordance for previously detected aberrations. A growing body of case reports and case series also demonstrates the opportunity for OGM to solve cases negative by next-generation sequencing analysis.

Publication	Summary of Key Points
Multisite Study of Optical Genome Mapping of Retrospective and Prospective Constitutional Disorder Cohorts Multicenter: Medical College of Wisconsin, University of Rochester Medical Center, Columbia University Medical Center, Greenwood Genetic Center, Praxis Genomics, H. Lee Moffit Cancer Center, University of Iowa Hospitals & Clinics, Medical College of Georgia, Augusta Unive Preprint: *medRxiv* 2022. Dec 31 doi: https://doi.org/10.1101/2022.12.26.22283900	• Multi-site, IRB approved publication as phase II of a larger study in constitutional postnatal disorders; total number of datapoints collected now over 1000 • OGM achieved 99.6% full or partial technical concordance with SOC method(s) and were fully concordant in 98.7% • Current phase focused on cohort of prospective (79) and autism spectrum disorder (ASD; 135) cases • 46.7% of ASD cases has SOC-only reported variants. Combining SOC and OGM found reportable variants in 61.5% of ASD cases, for a gain of 14.8% • 24.1% of prospective cases has SOC-only reported variants. Combining SOC and OGM found reportable variants in 34.2% of prospective cases, for a gain of 10.1%
Multisite evaluation and validation of Optical Genome Mapping for prenatal genetic testing Multicenter: Equanimitas, University of Cincinnati University of Rochester Medical Center, Greenwood Genetic Center, University of California San Francisco, Brigham & Women's Hospital, & Harvard Medical School, Columbia University Irving Medical Center, Quest Diagnostics Nichols Institute, Medical College of Georgia, Augusta University Preprint: *medRxiv* 2022. Dec 20. doi: https://doi.org/10.1101/2022.12.19.22283552	• Multicenter study with 16 authors across 9 institutes in the US • 200 data points representing 123 unique prenatal cases showed 100% concordance with standard of care, and 100% reproducibility between sites, operators and instruments • Many cases were tested in a tiered, sequential fashion using multiple SOC cytogenetic tests (KT, CMA, and FISH). 56% of cases had two SOC tests performed to reach a diagnosis and 19% required three • OGM accurately determined the genomic structure in a single test rather than up to 3 SOC tests. Additionally, the results are called by the software and did not require manual investigation. • 56% of cases (69/123) had two SOC tests performed to reach a diagnosis and 19% of cases (23/123) required three different SOC techniques • Case study highlighted required three sequential cytogenetic tests (KT, CMA and FISH) to determine the genomic structure, while OGM accurately predicted the structure in a single test

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30556_Rev. B_Constitutional Genetic Disorders Key Publications 01/31/2023

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Clinical validation and diagnostic utility of optical genome mapping in prenatal diagnostic testing Kolhe Lab Augusta University Preprint: *medRxiv*. 2022 May 16. doi: https://doi.org/10.1101/2022.05.11.22274975	• Retrospective validation study analyzing 94 unique amniocentesis samples previously characterized with karyotyping, FISH, and/or CMA • OGM was 100% concordant with findings from traditional cytogenetics across multiple types of chromosomal aberrations (aneuploidies, triploidy, deletions, duplications, translocations, isochromosomes, markers, AOH) • OGM detected 64 additional reportable SVs in 43 samples of 101 samples
Application of full-genome analysis to diagnose rare monogenic disorders Shieh, Penon-Portmann, and Wong Labs University of California – San Francisco *Genom 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
Optical genome mapping enables constitutional chromosomal aberration detection El Khattabi and Hoischen Labs Université de Paris, Hôpital Cochin Radboud University Medical Center *Am J Hum Genet*. 2021 Aug 5;108:1409-1422. doi: https://doi.org/10.1016/j.ajhg.2021.05.012	• 85 constitutional samples with known chromosomal aberrations in the context of developmental and reproductive disorders • OGM had 100% concordance with traditional cytogenetic methods of karyotyping, FISH, and chromosomal microarray, detecting 99/99 aberrations • Aberration types included 7 aneuploidies, 19 deletions, 20 duplications, 34 translocations, 6 inversions, 2 insertions, 6 isochromosomes, 1 ring chromosome and 4 complex

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Optical Genome Mapping: Analysis for Constitutional Genetic Disorders

Case Reports/Case Series

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

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 clinically confirmed 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 clinically diagnosed 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

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CASE REPORTS/CASE SERIES (CONT.)

Publication	Summary of Key Points
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 • Demonstrates the power of OGM and long-read sequencing to identify genomic variations in high-risk cancer-predisposing genes that are refractory to detection with traditional techniques
Detection of a mosaic *CDKL5* deletion and inversion by optical genome mapping ends an exhaustive diagnostic odyssey Shashi Lab Duke University Medical Center (part of the Undiagnosed Diseases Network) *Mol Genet Genomic Med.* 2021 Jul;9(7):e1665. doi: https://doi.org/10.1002/mgg3.1665	• Case report of a 4-year-old male with an epileptic encephalopathy of undiagnosed molecular origin • Extensive prior metabolic and genetic testing had been non-diagnostic, including chromosome analysis, CMA (Affymetrix Cytoscan HD array), an infantile epilepsy panel (sequencing and deletion/duplication analysis of 38 genes), mitochondrial genome sequencing, trio WES, and trio WGS • OGM identified a mosaic, de novo 90 kb deletion and inversion on the X chromosome disrupting the CDKL5 gene, resulting in a diagnosis of X-linked dominant early infantile epileptic encephalopathy-2 after confirmation in a clinical laboratory • Demonstrates the use of OGM to identify a mosaic structural variant missed by other techniquesassociated with a typical Marfan syndrome presentation

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