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*Original Paper*

# Optical Genome Mapping —A Cytogenomic Tool for Prenatal Diagnostics

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***Abstract***

*Chromosome aberration is the main cause of human inherited diseases. The routine clinical tests still rely on the standardization of cellular genetics. In recent years, Optical Genome Mapping (OGM) has been developed as a high-view method to detect large-scale structural variation of human genome. It is capable of detecting structural variations which are difficult to be detected by other methods. OGM preliminarily applied in the comprehensive identification of genomic structural variations, the visual delineation of chromosomal rearrangement patterns, and the diagnosis of some dynamic mutation diseases. This review primarily focuses on the technical attributes of OGM and its application in the field of prenatal diagnosis.*

***Keywords***

*Optical Genome Mapping, structural variation, Prenatal Diagnostics, cytogenomic*

## 1. Introduction

OGM (Optical Genome Mapping) is a new genome-wide technique based on nanochannels, which uses specific sequence sites in the genome to directly fluorescentially label macromolecular DNA, realizing linear optical imaging of DNA molecules, and has unique advantages in identifying structural variations of the genome. Genomic structural variation (SVs) is an important part of genetic polymorphism and an important cause of some diseases. When a part of an individual's DNA is

different from that of another individual in the same location, and the molecular length is greater than 1KB, we usually call this a structural variation in the genome (Rao et al., 2023). The structural variation of the genome includes inversion, translocation, deletion, replication and insertion. Deletion and replication are also known as copy number variations (CNVs). Structural variation has been shown to be an important source of human genetic diversity and disease susceptibility (Xu et al., 2023). The continuous advancement of high-throughput sequencing technology has led to a consistent reduction in the cost of genome sequencing, while also significantly enhancing the speed of sequencing. SVs functions by affecting the genome sequence, especially related genes (Goumy, Ouedraogo, et al., 2023).Therefore, the functional analysis of genes affected by genomic structural variation is of great significance for the analysis of the function of structural variation itself.

In 2021, researchers at Radboud University Medical Center and other institutions in the Netherlands developed OGM that can quickly, efficiently and accurately detect chromosomal and DNA abnormalities. The principle is to use a fluorescence transfer enzyme to specifically label a six-base sequence motif (CTTAAG) in the genome, resulting in green fluorescence. The DNA backbone is then stained blue, resulting in a series of blue DNA molecules with green fluorescence signals. The DNA molecules are linearized using a special structure on the chip, passed through nanopores in an electrophoresis-driven manner, and imaged. The genome is then assembled using software, and compared to the reference genome map. OGM eliminates the need for cell culture and enables rapid generation of precise and high-resolution genome-wide restriction maps using single DNA molecules based on genomic restriction enzyme patterns,10000 times higher resolution than karyotype analysis.

## 2. Common Prenatal Diagnostic Techniques

### *2.1 G-banding Chromosome Karyotype Analysis*

G-banding chromosome karyotype analysis has been the most common method for diagnosing chromosomal abnormalities (Howe, Umrigar, & Tsien, 2014). This method involves culture of cells or tissues under sterile conditions, and chromosome specimens are prepared by a series of operations such as trypsin digestion and Giemsa staining, and chromosome morphology can be observed under a microscope for karyotype analysis. Chromosomal karyotype analysis is suitable for diseases with high degrees of quantitative and structural dysplasia, such as phylogenetic diseases, but the total body diagnosis rate is much lower than 10%. However, there are myriad factors involved in the whole culture and analysis process, such as culture environment, colchicine concentration and action time, hypotonicity, fixation, drip, trypsin digestion, Giemsa staining, etc. Currently, there is no unified quality control for experimental manipulation of chromosome preparation. At the same time, this method has elevated requirements for laboratory technicians, and karyotype reading has a certain subjectivity.

### *2.2 Chromosomal Microarray Analysis (CMA)*

CMA has the capability to identify clinically significant genomic copy number variants (CNVs). In

addition to numerical chromosomal abnormalities, newborn fetuses may also inherit copy number variations (CNVs) or acquire loss of heterozygosity (LOH) from their parents' genomes, which can exert detrimental effects on embryonic or fetal development(X. Liu, Liu, Wang, & Hu, 2022). However, aCGH probes cannot cover all chromosome segments, and cannot detect polyploidy and low-proportion mosaicism. Most current clinical CMA platforms can detect copy number changes in the whole genome with a lower limit of resolution of about 400kb, which is more than 10-fold higher than G-banding karyotype analysis (Franco-Jarava et al., 2022). The American Congress of Obstetricians and Gynecologists (ACOG) has issued guidelines recommending the application of CMA for genetic testing in prenatal diagnosis of abnormal fetuses, while highlighting that CMA testing can also be conducted for normal fetuses if other interventional prenatal diagnostic procedures are carried out due to other factors (Xiang et al., 2020).

*2.3 Next-generation Sequencing (NGS)*

NGS also known as high-throughput sequencing, has the characteristics of high throughput, low cost, fast speed, and has been widely used in the field of genetic disease detection in recent years. It employs the principle of "sequencing while synthesizing," enabling the parallel sequencing of hundreds of thousands or even millions of DNA molecules simultaneously, thus making it appropriate for challenging cases where the genetic mutation sites are unclear. NGS encompasses whole genome sequencing (WGS), whole exome sequencing (WES), as well as Panel targeted sequencing, among others. WES is capable of detecting exonic gene sequence variations throughout the entire genome, which represents the protein-coding region, notwithstanding that it constitutes merely 1% of the genome. However, it is currently postulated that 85% of disease-causing gene mutations transpire in this region, rendering it one of the most prevalently utilized gene sequencing techniques in clinical practice. WGS covers the entire DNA sequence of the genome, including exons, introns, and gene regulatory sequences. However, there are also certain limitations to second-generation sequencing, with read lengths being too short and the operational procedures being complex. CNV-seq involves sequencing samples and comparing the sequencing outcomes with the human reference genome, followed by the identification of CNV through bioinformatics analysis. By adjusting the sequencing depth and varying the resolution, it is capable of detecting CNVs of different magnitudes. Numerous reports have utilized the CNV-seq to analyze the association between CNV and miscarriage (Chen et al., 2021; S. Liu et al., 2015; Sheng et al., 2021; Y. Wang et al., 2020; X. Zhang, Huang, Yu, & Wu, 2021). However, CNV-seq cannot detect subclonal events or balanced chromosomal aberrations below 5%-20%, and cannot distinguish between reciprocal and translocation events.

*2.4 Fluorescent in Situ Hybridization (FISH)*

FISH is a cytogenetic technique that utilizes the complementary base pairing property to hybridize fluorescently labeled probes with tissue, cell nuclei, or chromosomal DNA to qualitatively, quantitatively, and spatially locate the target nucleic acid in cells, thereby clearly revealing the complex and subtle chromosomal aberrations or genetic mutations in cells (Klinger et al., 1992). It exhibits the

characteristics of high specificity and rapid detection speed, and is prevalently employed in prenatal diagnosis (Caine, Maltby, Parkin, Waters, & Crolla, 2005). It can detect smaller fragments of deletions, duplications, and balanced translocations, but requires pre-determining the chromosomal segments to be tested and preparing corresponding probes.

Each technique has advantages and limitations. Conventional karyotyping can only detect structural chromosomal abnormalities larger than 5Mb, which limits its detection ability. FISH can detect smaller deletions, duplications and balanced translocations, but the chromosome fragments to be tested need to be determined in advance to prepare corresponding probes. SNP-array is the preferred method for detecting chromosomal abnormalities and CNV, but it cannot detect inversion, balanced translocation and other variations that do not change the copy number of the genomic region. Due to the short read length, the ability of next-generation sequencing to detect structural variations in repetitive regions of the genome is very limited, and it is biased to detect SV, which may miss many important SVS.

## 3. Application of OMG in Prenatal Diagnosis

OGM uses specific sequence sites in the genome to fluorescently label large DNA molecules without fragmentation, amplification, and modification, allowing direct labeling for linear optical imaging. The average read length exceeds 200 kbp, thereby enabling the concurrent detection of multiple disparate types of gene structural mutations at one time, encompassing deletions, translocations, inversions, duplications, insertions, ring chromosomes, complex rearrangements, and isochromosomes, among others (Gerding et al., 2022).

### *3.1 Detection of Genomic Structural Variation*

The current trend in gene-based SV detection is the gradual adoption of OGM, thanks to its long read length and high resolution. Levy-Sakin et al. used OGM to analyze large SV(>2kb) from 154 individuals in the 1000 Genomes Project in 2019, and found that this technology increased the detection rate of large insertions and deletions by 8.5 times and 35%, respectively, which confirmed the role of OGM in SV Great potential in testing (Levy-Sakin et al., 2019). The Human Genome Structural Variation Consortium combined the application of sequencing technology and OGM to assemble the human genome of 64 haplotypes from 32 individuals. For SV, third-generation sequencing detected only 72% of the large SV fragments (larger than 5kb) suggested by OGM, whereas OGM detected an additional 1175 unique SV sites (Levy-Sakin et al., 2019).

There have been many studies that have analyzed the detection efficiency of OGM. Some scholars conducted OGM detection on 85 samples with clearly defined mutation types and found that in the analysis of chromosomal mutations that did not involve the centromere region, the detection results of OGM and conventional genetic testing methods were consistent (Mantere et al., 2021). They believe that OGM, with its comprehensive. detection range and superior detection efficiency, has the potential to be a reliable alternative to karyotyping, FISH, and CMA. In a double-blind, retrospective study on 94 prenatal samples, the feasibility and effectiveness of OGM in prenatal diagnosis were investigated

(Bouassida et al., 2024). The results of OGM were completely consistent with those of standard methods (Iqbal et al., 2023).Although OGM can provide additional genetic information such as breakpoint interval and rearrangement pattern for samples with mutation, it also misses the detection of large fragment inversions and microdeletions in the subtelomeric region of X chromosome (Barseghyan et al., 2024; Dremsek et al., 2021; Levy et al., 2024). OGM is capable of detecting aneuploidy, copy number variations and other structural variants, including balanced and unbalanced rearrangements ranging from thousands of base groups to several trillion base groups (Q. Zhang et al., 2023). It is considered that there is still space for improvement of OGM algorithm. More research data and application experience need to be accumulated before OGM can be used in clinical practice.

*3.2 Detection of Complex Chromosomal Rearrangements (CCR)*

CCR refers to a chromosomal structural abnormality involving at least two chromosomes with three or more breakpoints (Pellestor et al., 2011). Genomic instability has continuously driven the occurrence of mutations during the evolution of the human genome. Chromosomal rearrangements caused by mechanisms such as non-allelic homologous recombination, non-homologous end joining, replication errors, and long scattered repeats mediated retrotransposition are pathogenic mainly by causing changes in genome dosage, causing gene destruction or fusion, and affecting gene regulation (Hao et al., 2022; H. Wang et al., 2023). OGM performed on a woman with an adverse pregnancy history and her fetus, and CCR between chromosomes 6, 12 and 15 was found in the pregnant woman, and the position and direction of the translocation fragment insertion were clarified, which provided detailed genetic information for the patient's genetic counseling and pregnancy guidance (Yang & Hao, 2022).

At present, researchers are facing the following difficulties in the identification and pathogenicity assessment of chromosomal rearrangements. First, conventional techniques have limited ability to detect occult balanced translocations and complex structural rearrangements. Second, in order to reconstruct the rearrangement pattern, the orientation and position of the inserted fragment are usually determined. It requires the combined application of multiple detection methods, so it is time-consuming and laborious. Finally, it is another challenge to precisely locate the breakpoints and determine whether the breakpoints involve genes (Barseghyan et al., 2023). Although occult balanced translocations do not cause changes in genetic material dosage, they are closely related to adverse pregnancy history and infertility, and may lead to monogenic diseases when the translocation breakpoints involve genes (Mathew & Akkari, 2024). It is possible for OGM to simultaneously detect all types of chromatic aberrations using a single detection platform (Z. Zhang et al., 2024). In addition, OGM can provide the orientation and positioning of the reconstructed segments, which is of great importance in prenatal diagnosis.

*3.3 Diagnosis of Disease with Specific Dynamic Mutations and Rare Chromosomal Structural Variants*

Facioscapulohumeral muscular dystrophy-1(FSHD-1) is a genetic disease of the neuromuscular system caused by the deletion of the D4Z4 repeat unit in the 4q35 region. The age of onset, course and severity of the disease vary greatly, and the penetrance of the disease is incomplete. The penetrance increases

with age and the shortening of the repetitive units (Vincenten et al., 2022). The diagnosis of FSHD-1 is still mainly based on Southern blot hybridization, but this method requires high technical requirements for experimental personnel and can only perform semi-quantitative analysis. OGM can visually depict D4Z4 repeat units through visual optical maps. The main advantage of OGM is that it can distinguish 4qA and 4qB haplotypes and avoid interference of 10q26 homologous sequences (Zheng et al., 2020). Its characteristics of automation and high throughput greatly improve the detection efficiency.

OGM could identify the position and direction of repeat insertion. The pathogenicity of chromosomal microduplications may be associated with threefold dose sensitivity, intragenic duplication leading to reading frame disruption, intergenic duplication breakpoints disrupting genes, or resulting in gene fusions. OMG can detect not only unbalanced but also structural variations within the range of balanced gene groups with high precision. Newman et al. reported that 17% of the repeats are not tandem repeats but complex rearrangements, such as insertional translocations, which lead to gene fusion or disruption and produce a clinical phenotype (Newman, Hermetz, Weckselblatt, & Rudd, 2015). OGM possesses distinct advantages in detecting occult chromosomal rearrangement variants, making it a promising new clinical first-line method for identifying occult balanced chromosomal rearrangements. In terms of discrimination of SVs, OGM and array ratio are comparable to gene group hybridization (aCGH). The advantages of OGM compared with aCGH are that it can detect structural variation of balance, locate materials outside the frontal area, and locate fault points with high discrimination rate.

## 4. Limitations of OGM

As a new genetic testing technology, OGM has many advantages, but it also entails certain drawbacks. The major impediment to the application of OGM in prenatal diagnosis is the time-consuming microculture process. The OGM workflow includes ultra-high fraction DNA extraction, fraction labeling, Saphyr core running and data analysis, all of which can be completed within 4-6 days (Goumy, Guy Ouedraogo, et al., 2023). OGM still has high requirements for prenatal samples, and direct DNA extraction using uncultured amniotic fluid samples is not possible.

Although OGM is one of the next generation cytologic techniques, it has a high discrimination rate and can detect all types of staining in a single test. However, its application in prenatal diagnosis is still limited. The detection of balanced breakpoints in large, repetitive, nonreflective regions, such as centromeres, short arms of nontelomeric chromosomes, or compositional metachromatic domains, has not yet been performed with the use of ocular techniques (Dremsek et al., 2021). OGM is the most promising technology to replace karyotype analysis, but OGM is still insufficient in the detection of telomere, centromor and heterochromatin regions, and the cost is relatively high, OGM has not been applied on a large scale like karyotype analysis (Q. Zhang et al., 2023).

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**References**

Barseghyan, H., Eisenreich, D., Lindt, E., Wendlandt, M., Scharf, F., Benet-Pages, A., . . . Koehler, U. (2024). Optical Genome Mapping as a Potential Routine Clinical Diagnostic Method. *Genes (Basel)*, *15*(3). http://doi.org/10.3390/genes15030342

Barseghyan, H., Pang, A. W. C., Clifford, B., Serrano, M. A., Chaubey, A., & Hastie, A. R. (2023). Comparative Benchmarking of Optical Genome Mapping and Chromosomal Microarray Reveals High Technological Concordance in CNV Identification and Additional Structural Variant Refinement. *Genes (Basel)*, *14*(10). http://doi.org/10.3390/genes14101868

Bouassida, M., Molina-Gomes, D., Koraichi, F., Hervé, B., Lhuilier, M., Duvillier, C., . . . Vialard, F. (2024). The clinical value of optical genome mapping in the rapid characterization of RB1 duplication and 15q23q24.2 triplication, for more appropriate prenatal genetic counselling. *Mol Genet Genomic Med*, *12*(4), e2437. http://doi.org/10.1002/mgg3.2437

Caine, A., Maltby, A. E., Parkin, C. A., Waters, J. J., & Crolla, J. A. (2005). Prenatal detection of Down's syndrome by rapid aneuploidy testing for chromosomes 13, 18, and 21 by FISH or PCR without a full karyotype: a cytogenetic risk assessment. *Lancet*, *366*(9480), 123-128. http://doi.org/10.1016/s0140-6736(05)66790-6

Chen, L., Wang, L., Tang, F., Zeng, Y., Yin, D., Zhou, C., . . . Wang, J. (2021). Copy number variation sequencing combined with quantitative fluorescence polymerase chain reaction in clinical application of pregnancy loss. *J Assist Reprod Genet*, *38*(9), 2397-2404. http://doi.org/10.1007/s10815-021-02243-9

Dremsek, P., Schwarz, T., Weil, B., Malashka, A., Laccone, F., & Neesen, J. (2021). Optical Genome Mapping in Routine Human Genetic Diagnostics-Its Advantages and Limitations. *Genes (Basel)*, *12*(12). http://doi.org/10.3390/genes12121958

Franco-Jarava, C., Valenzuela, I., Riviere, J. G., Garcia-Prat, M., Martínez-Gallo, M., Dieli-Crimi, R., . . . Colobran, R. (2022). Common Variable Immunodeficiency and Neurodevelopmental Delay Due to a 13Mb Deletion on Chromosome 4 Including the NFKB1 Gene: A Case Report. *Front Immunol*, *13*, 897975. http://doi.org/10.3389/fimmu.2022.897975

Gerding, W. M., Tembrink, M., Nilius-Eliliwi, V., Mika, T., Dimopoulos, F., Ladigan-Badura, S., . . . Vangala, D. B. (2022). Optical genome mapping reveals additional prognostic information compared to conventional cytogenetics in AML/MDS patients. *Int J Cancer*, *150*(12), 1998-2011.

http://doi.org/10.1002/ijc.33942

Goumy, C., Guy Ouedraogo, Z., Soler, G., Eymard-Pierre, E., Laurichesse, H., Delabaere, A., . . . Tchirkov, A. (2023). Optical genome mapping for prenatal diagnosis: A prospective study. *Clin Chim Acta*, *551*, 117594. http://doi.org/10.1016/j.cca.2023.117594

Goumy, C., Ouedraogo, Z. G., Bellemonte, E., Eymard-Pierre, E., Soler, G., Perthus, I., . . . Tchirkov, A. (2023). Feasibility of Optical Genome Mapping from Placental and Umbilical Cord Sampled after Spontaneous or Therapeutic Pregnancy Termination. *Diagnostics (Basel)*, *13*(23). http://doi.org/10.3390/diagnostics13233576

Hao, N., Zhou, J., Li, M. M., Luo, W. W., Zhang, H. Z., Qi, Q. W., . . . Liu, J. (2022). [Efficacy and initial clinical evaluation of optical genome mapping in the diagnosis of structural variations]. *Zhonghua Yu Fang Yi Xue Za Zhi*, *56*(5), 632-639. http://doi.org/10.3760/cma.j.cn112150-20220212-00131

Howe, B., Umrigar, A., & Tsien, F. (2014). Chromosome preparation from cultured cells. *J Vis Exp*, (83), e50203. http://doi.org/10.3791/50203

Iqbal, M. A., Broeckel, U., Levy, B., Skinner, S., Sahajpal, N. S., Rodriguez, V., . . . Kolhe, R. (2023). Multisite Assessment of Optical Genome Mapping for Analysis of Structural Variants in Constitutional Postnatal Cases. *J Mol Diagn*, *25*(3), 175-188. http://doi.org/10.1016/j.jmoldx.2022.12.005

Klinger, K., Landes, G., Shook, D., Harvey, R., Lopez, L., Locke, P., . . . et al. (1992). Rapid detection of chromosome aneuploidies in uncultured amniocytes by using fluorescence in situ hybridization (FISH). *Am J Hum Genet*, *51*(1), 55-65.

Levy-Sakin, M., Pastor, S., Mostovoy, Y., Li, L., Leung, A. K. Y., McCaffrey, J., . . . Kwok, P. Y. (2019). Genome maps across 26 human populations reveal population-specific patterns of structural variation. *Nat Commun*, *10*(1), 1025. http://doi.org/10.1038/s41467-019-08992-7

Levy, B., Liu, J., Iqbal, M. A., DuPont, B., Sahajpal, N., Ho, M., . . . Stevenson, R. E. (2024). Multisite Evaluation and Validation of Optical Genome Mapping for Prenatal Genetic Testing. *J Mol Diagn*. http://doi.org/10.1016/j.jmoldx.2024.06.006

Liu, S., Song, L., Cram, D. S., Xiong, L., Wang, K., Wu, R., . . . Yang, F. (2015). Traditional karyotyping vs copy number variation sequencing for detection of chromosomal abnormalities associated with spontaneous miscarriage. *Ultrasound Obstet Gynecol*, *46*(4), 472-477. http://doi.org/10.1002/uog.14849

Liu, X., Liu, S., Wang, H., & Hu, T. (2022). Potentials and challenges of chromosomal microarray analysis in prenatal diagnosis. *Front Genet*, *13*, 938183. http://doi.org/10.3389/fgene.2022.938183

Mantere, T., Neveling, K., Pebrel-Richard, C., Benoist, M., van der Zande, G., Kater-Baats, E., . . . El Khattabi, L. (2021). Optical genome mapping enables constitutional chromosomal aberration detection. *Am J Hum Genet*, *108*(8), 1409-1422. http://doi.org/10.1016/j.ajhg.2021.05.012

Mathew, M. T., & Akkari, Y. M. N. (2024). Optical Genome Mapping in Prenatal Diagnosis:

Democratizing Comprehensive Cytogenomic Testing. *Clin Chem*, *70*(6), 783-785. http://doi.org/10.1093/clinchem/hvae060

Newman, S., Hermetz, K. E., Weckselblatt, B., & Rudd, M. K. (2015). Next-generation sequencing of duplication CNVs reveals that most are tandem and some create fusion genes at breakpoints. *Am J Hum Genet*, *96*(2), 208-220. http://doi.org/10.1016/j.ajhg.2014.12.017

Pellestor, F., Anahory, T., Lefort, G., Puechberty, J., Liehr, T., Hédon, B., & Sarda, P. (2011). Complex chromosomal rearrangements: origin and meiotic behavior. *Hum Reprod Update*, *17*(4), 476-494. http://doi.org/10.1093/humupd/dmr010

Rao, H., Zhang, H., Zou, Y., Ma, P., Huang, T., Yuan, H., . . . Yang, B. (2023). Analysis of chromosomal structural variations in patients with recurrent spontaneous abortion using optical genome mapping. *Front Genet*, *14*, 1248755. http://doi.org/10.3389/fgene.2023.1248755

Sheng, Y. R., Hou, S. Y., Hu, W. T., Wei, C. Y., Liu, Y. K., Liu, Y. Y., . . . Zhu, X. Y. (2021). Characterization of Copy-Number Variations and Possible Candidate Genes in Recurrent Pregnancy Losses. *Genes (Basel)*, *12*(2). http://doi.org/10.3390/genes12020141

Vincenten, S. C. C., Van Der Stoep, N., Paulussen, A. D. C., Mul, K., Badrising, U. A., Kriek, M., . . . Lassche, S. (2022). Facioscapulohumeral muscular dystrophy-Reproductive counseling, pregnancy, and delivery in a complex multigenetic disease. *Clin Genet*, *101*(2), 149-160. http://doi.org/10.1111/cge.14031

Wang, H., Yang, Y., Yang, N., Wang, Y., Li, H., & Hu, W. (2023). [Optical genome mapping analysis of a Chinese pedigree with a rare chromosome 17 paracentric inversion insertion]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*, *40*(6), 727-732. http://doi.org/10.3760/cma.j.cn511374-20220107-00012

Wang, Y., Li, Y., Chen, Y., Zhou, R., Sang, Z., Meng, L., . . . Xu, Z. (2020). Systematic analysis of copy-number variations associated with early pregnancy loss. *Ultrasound Obstet Gynecol*, *55*(1), 96-104. http://doi.org/10.1002/uog.20412

Xiang, J., Ding, Y., Song, X., Mao, J., Liu, M., Liu, Y., . . . Wang, T. (2020). Clinical Utility of SNP Array Analysis in Prenatal Diagnosis: A Cohort Study of 5000 Pregnancies. *Front Genet*, *11*, 571219. http://doi.org/10.3389/fgene.2020.571219

Xu, P., Wang, L., Li, J., Huang, S., Gao, M., Kang, R., . . . Gao, Y. (2023). OGM and WES identifies translocation breakpoints in PKD1 gene in an polycystic kidney patient and healthy baby delivered using PGT. *BMC Med Genomics*, *16*(1), 285. http://doi.org/10.1186/s12920-023-01725-2

Yang, Y., & Hao, W. (2022). Identification of a familial complex chromosomal rearrangement by optical genome mapping. *Mol Cytogenet*, *15*(1), 41. http://doi.org/10.1186/s13039-022-00619-9

Zhang, Q., Wang, Y., Xu, Y., Zhou, R., Huang, M., Qiao, F., . . . Hu, P. (2023). Optical genome mapping for detection of chromosomal aberrations in prenatal diagnosis. *Acta Obstet Gynecol Scand*, *102*(8), 1053-1062. http://doi.org/10.1111/aogs.14613

Zhang, X., Huang, Q., Yu, Z., & Wu, H. (2021). Copy number variation characterization and possible candidate genes in miscarriage and stillbirth by next-generation sequencing analysis. *J Gene Med*, *23*(12), e3383. http://doi.org/10.1002/jgm.3383

Zhang, Z., He, S., Li, X., Cheng, K., Wei, Y., & Ren, Z. (2024). [Application of optical genome mapping technology for the detection of chromosomal structural variations]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*, *41*(3), 257-265. http://doi.org/10.3760/cma.j.cn511374-20230107-00013

Zheng, Y., Kong, L., Xu, H., Lu, Y., Zhao, X., Yang, Y., . . . Kong, X. (2020). Rapid prenatal diagnosis of Facioscapulohumeral Muscular Dystrophy 1 by combined Bionano optical mapping and karyomapping. *Prenat Diagn*, *40*(3), 317-323. http://doi.org/10.1002/pd.5607