NEWSLETTER

This newsletter centers on reproductive topics with a genetics focus. If there is an organization or upcoming webinar you'd like me to include in a future newsletter, please feel free to reach out at genetics@modernreproduction.org.

Sign up for the newsletter here

Webinars:

GENOMIC PREDICTION: FROM RESEARCH TO REAL WORLD: NYU STUDY
4/4/24 @ 3PM EST

Register

PROGENESIS: MANAGEMENT OF UNEXPLAINED INFERTILITY
4/10/24 @ 7:30AM EST

Register

GENE-DISEASE VALIDITY: DEVELOPING AND APPLYING A RIGOROUS FRAMEWORK IN A DIAGNOSTIC LABORATORY

On Demand

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NEWSLETTER

The little lit review

1 Exploring the factors affecting classification and reporting of uncertain prenatal microarray findings, using a "virtual fetus"model-a pilot study

Rachel Michaelson-Cohen | Liat Sheelo Salzer | Dana Brabbing-Goldstein | Yuval Yaron | Adi Reches | Hagith Yonath | Miriam Regev | Hagit Shani | Gheona Altarescu | Reeval Segel | Rivka Sukenik-Halevy | Hagit Daum | Tamar Harel | Vardiella Meiner | Lina Basel-Salmon | Lena Sagi-Dain | Idit Maya

What an interesting study: the authors identified 10 copy number variants (CNVs) from a hospital database in which the CNvs were classified as variants of uncertain significance (VUS), prenatally detected, inherited by an apparently healthy parent, normal ultrasound/biochemical markers, and >1Mb in size. They asked 15 geneticists to classify the variants by providing them with this information and followed up with a few questions regarding their opinions if the VUS should be reported to patients and what follow up testing (prenatal or preimplantation genetic testing) would be made available.

TABLE 1 Classification, reporting and management per examined copy number variant.

CNV coordinates (*GRCH37/HG19)	Classification *N* (%)			Decision to report (%)	Indication for invasive testing (%)	Indication for IVF-PGT (%)
	LB	VUS	LP/P			
arr2p14(chr2:67,172,786-68,235,717)x3	11 (73.3)	4 (26.7)	-	26.7	0	0
arr2p16.2(chr2:54,823,728-56,422,476)x3	2 (13.3)	13 (86.7)	-	80	20	6.7
arr6q25.3(chr6:157,259,731-158,865,369)x3	1 (6.7)	11 (73.3)	3 (20)	93.3	33.3	33.3
arr12p13.33 (chr12:230,451-2,162,724)x3	-	15 (100)	-	100	20	13.3
arr13q14.12-q14.2(chr13:45691164-48538608)x3	-	15 (100)	-	80	26.7	0
arr2q32.2q32.3(chr2:191,514,718-192,541,906)x1	1 (6.7)	9 (60)	5 (33.3%)	93.3	46.7	33.3
arr5q31.3q32(chr5:142,768,031-145,425,648)x1	1 (6.7)	12 (80)	2 (13.3%)	86.7	53.3	40
arr7q21.1(chr7:83,347,955-85,365,821)x1	-	12 (80)	3 (20)	86.7	46.7	53.3
arr7p22.3(chr7:43,376-1,459,209)x1	-	11 (73.3)	4 (26.6)	100	53.3	40
arr11p15.4(chr11:4,751,811-6,852,987)x1	-	10 (66.7)	5 (33.3)	93.3	53.3	46.7

Note: Each CNV was classified by all 15 interpreters as either LB, VUS, LP or P. The table shows number of interpreters giving each classification for each variant (N, %), and frequency of decision of interpreters to report to patient, to recommend invasive testing (standard amniocentesis at 17–19 weeks) and to recommend IVF-PGT for each CNV.

Abbreviation: CNV, copy number variant; IVF, in vitro fertilization; LB, likely benign; LP, likely pathogenic; N, number; P, pathogenic; PGT, pregestational testing; VUS, variant of uncertain significance.

6/10 of the variants were classified as likely pathogenic or pathogenic at least once by the group of geneticists, which would have impacted patient care. Classification depended on the geneticists' specialization and experience. Recommendations were also influenced by these factors. Not only do classification and recommendations vary, but reporting of findings differ. Lab policies and scientist opinions often determine what is even being reported out to patients. Consensus is needed in all of these areas as this study demonstrates the variability of classification and recommendations.

1% of apparent normal u/s and biochem have clinically significant CMA findings whereas 0.4-6% have VUS

Deletions/paternally inherited variants raised more suspicion of pathogenicity than duplications and maternally inherited variants.

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New(er) test methodology: **optical genome mapping**

Optical genome mapping evaluates cytogenetic aberrations such as including aneuploidies, deletions, duplications, balanced and unbalanced events (translocations, inversions, and insertions), AOH regions, and triploid genomes with similar detection rates than conventional cytogenetic tests: FISH, karyotype, and microarray. This test has been implemented in postnatal period and is moving to investigations in the prenatal realm.

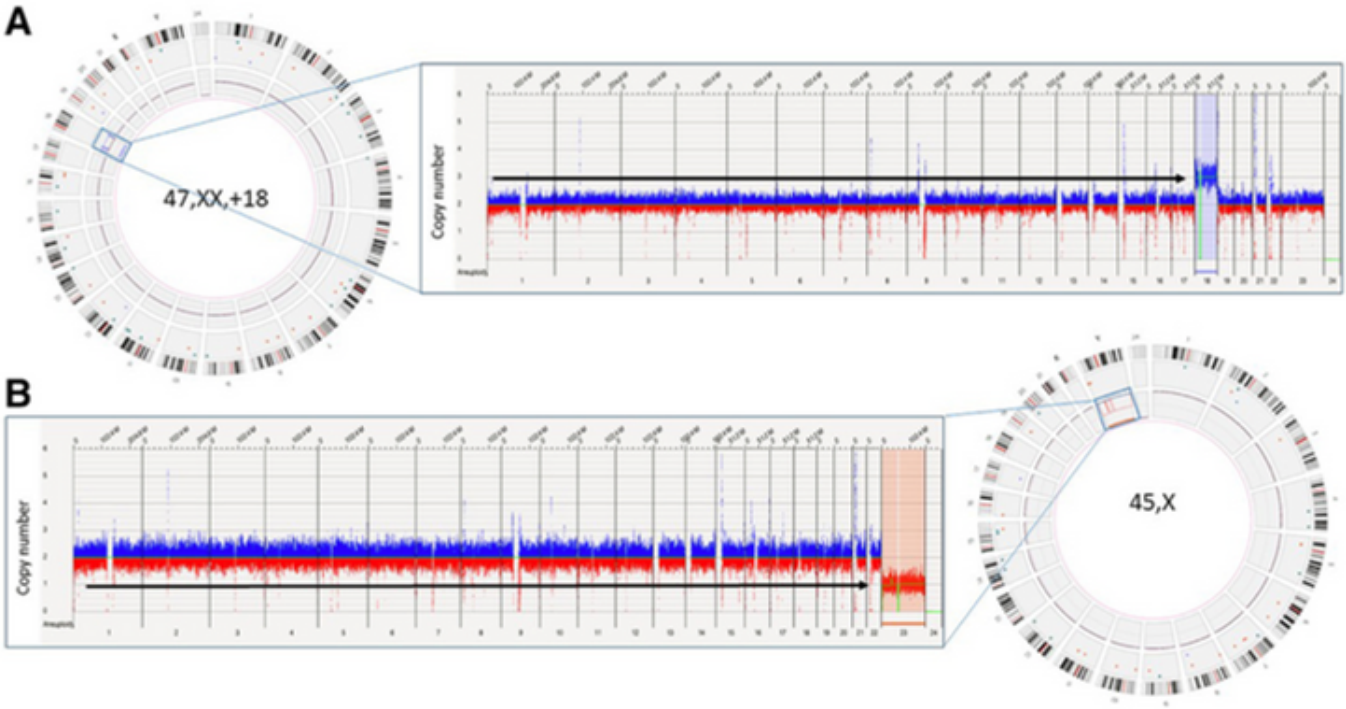

Figure 2 Representative example of aneuploidy detection with optical genome mapping. **A: Left panel:** The circos plot with a copy number gain visible and highlighted with a **blue boxed area** on the circos plot around the inner circle of the copy number variation (CNV) track of chromosome 18. **Right panel:** The whole genome CNV profile where the *y* axis shows the copy number state and aneuploidy caller, and the *x* axis shows the chromosome number. The copy number gain and aneuploidy call are observed on chromosome 18. **B: Right panel:** The circos plot with a copy number loss visible and highlighted with a **blue boxed area** on the circos plot around the inner circle of the CNV track of chromosome X. **Left panel:** The loss of chromosome X to a copy number state of 1 and an aneuploidy call observed for chromosome X on the whole genome CNV profile visualization.

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2 Clinical Validation and Diagnostic Utility of Optical Genome Mapping in Prenatal Diagnostic Testing

Nikhil S. Sahajpal, Ashis K. Mondal,y Timothy Fee, Benjamin Hilton, Lawrence Layman, Alex R. Hastie, Alka Chaubey, Barbara R. DuPont, and Ravindra Kolhe

The article explores the clinical validation and diagnostic utility of optical genome mapping with conventional cytogenetic tests on cultured amniocytes. Ultimately, concordance was 100% and OGM identified variants that were otherwise missed by conventional testing including conditions such as intellectual disability, Klippel-Feil syndrome 3, spinocerebellar ataxia 1, and others.

Cell culture was needed for OGM, which does not differ from the need of cell culture for karyotype and occasionally for microarray, as direct DNA analysis may not be possible with some sample sizes.

The authors end with the recommendation: "Because OGM can detect the different classes of SVs and alleviates the need for multiple tests (karyotyping and CMA), it is recommended that after a negative FISH test result on direct amniocytes, the sample should be tested with OGM instead of karyotyping and/or CMA."

3 Analysis of chromosomal structural variations in patients with recurrent spontaneous abortion using optical genome mapping

Huihua Rao, Haoyi Zhang, Yongyi Zou, Pengpeng Ma, Tingting Huang , Huizhen Yuan, Jihui Zhou, Wan Lu, Qiao Li, Shuhui Huang, Yanqiu Liu, Bicheng Yang

The article explores optical genome mapping in the setting of couples with recurrent miscarriages and POCs with chromosomal abnormalities. 7 couples who had miscarriages, confirmed with chromosomal abnormalities, underwent optical genome mapping via blood analysis. OGM identified variants that a karyotype would have as well as additional complex chromosomal rearrangement (CCRs) and four cryptic balanced reciprocal translocations (BRTs). "Cryptic BRTs are SVs that do not obviously change chromosome banding or the translocation segments are below the karyotyping limit. Indeed, they are undetected by standard-of-care tests and may be underestimated." There have been at least one report of PGT results that indicate a rearrangement in one genetic contributor, but initial karyotype was normal. Until, a reevaluation was completed, with specific breakpoints to investigate, was a cryptic BRT identified for the patient.

TABLE 1 Patient demographics, karyotypes, and CNVs of miscarriage tissues.

Patient	Gender	Karyotype	Patient age in years	Partner age in years	Miscarriages	CNVs of miscarriage tissue (GRCh38/hg38)
01	Male	46,XY,t(3;8)?(q28;p22)	33	30	2	6q25.1(149,547,655-150,890,234) × 1 (VOUS)* 8p23.3p22(1,710,455-13,638,023) ×3 (P)
02	Male	46,XY,inv(7)(q31.3q32)t(7;17)(q31.3;q25)	30	29	3	—
03	Female	46,XX,t(10;16)(p13;q24)	38	40	2	10q26.12q26.3(120,725,578-133,612,882) × 1 (P) 16q23.2q24.3(80,632,478-90,088,654) × 3 (P)
04	Female	46,XX	31	32	2	13q14.2q34(49883309-114344353) × 1 (P) 14q21.2q32.33(45360061-106851686) × 3 (P)
05	Male	46,XY	31	31	2	6q25.3q27(159,326,441-170,605,209) × 3 (LP)
06	Female	46,XX	32	32	3	1q42.2-q44(231,267,102-249,240,147) × 3 (P) 11q23.3-q25(119,548,730-134,945,944) × 1 (P)
07	Male	46,XY	33	31	2	1p36.33p36.32(914087-2544379) × 3 (LP) 9q34.3(137002730-138124196) × 1 (P)

*The deletion inherited from the partner.

	karyotype	OGM result
04	46,XX	ogm[GRch38]t(13;14)(q14.2;q21.2)
05	46,XY	ogm[GRch38]t(2;6)(q37.3;q25.3)
06	46,XX	ogm[GRch38]t(1;11)(q42.2;q23.3)
07	46,XY	ogm[GRch38]t(1;9)(p36.32;q34.3)

NEWSLETTER

Community Content:

Donor Conception Network has upcoming events both directed to healthcare professionals and patients.

Modern Reproduction Content:

Handouts and brochures are available on the site such as this prenatal diagnostic handout that might need to include optical genome mapping soon ! :D