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Suspected maternal mosaic trisomy 8: insights into this uncommon finding on cell-free DNA screening

Sophie Crowdes, MS, CGC; Brittany Dyr, MS, CGC; Erica Soster, MS, LCGC; Karen Compton, MMSc, CGC; Vivian Weinblatt, MS, CGC
Labcorp Women's Health and Genetics, Laboratory Corporation of America® Holdings, San Diego, CA

1. Introduction

Since its introduction in 2011, genome-wide cell-free DNA (GW-cfDNA) screening has evolved to allow for the detection of chromosomal events outside of the scope of common aneuploidies, including suspected maternal findings. One finding detectable by GW-cfDNA is mosaic trisomy 8 (mT8), as both a fetal and maternal finding. mT8 can be either constitutional or acquired throughout an individual's lifetime. Given its tendency to be tissue-specific, features of constitutional mT8 are highly variable; affected individuals may be clinically asymptomatic or may present with features such as intellectual disability, congenital heart defects, and kidney malformations.[1] In some patients, trisomic cells may predominate in lymphocytes and either not be found or appear in small proportion in other tissues. No clear correlation has been determined between the proportion of trisomic cells and clinical manifestations.[2]

Trisomy 8 is a common cytogenetic finding in myelodysplastic syndromes (MDS) and hematological malignancies, representing the sole cytogenetic change in approximately 5% of acute myeloid leukemia cases and approximately 10% of MDS cases, in addition to being commonly found in chronic myeloproliferative disorders.[3-5] Trisomy 8 related to MDS and malignancy is presumed to be predominantly acquired rather than constitutional; however, constitutional mT8 appears to be associated with an increased risk for these conditions as well.[3,6]

2. Methods

A retrospective review of cases with suspected maternal mT8 was conducted from clinical samples on both the traditional platform (reporting on chromosomes 13, 18, and 21, with the option of including analysis for sex chromosome aneuploidies, chromosomes 16 and 22, and select microdeletions) and a genome-wide cfDNA platform performed at one laboratory. Outcome data was collected from the ordering provider when available and/or cross-referenced and matched with diagnostic testing performed internally at the same laboratory.

Referral indications were retrieved from the test requisition and/or by calculating the patient's age at the time of delivery to categorize them as advanced maternal age if over 35 years of age. The multiple indications category included cases with two or more high-risk indications.

3. Results

Suspected maternal mT8 was identified in cfDNA sequencing data of 28 separate patients between December 2014 and November 2021. Five patients had two separate samples analyzed at our laboratory, both producing the same result regardless of whether the second sample was from the same or a different pregnancy. Traditional analysis was requested in approximately 73% (24/33) of total cases, while genome-wide analysis was requested in the other 27% (9/33) of cases. Samples requested for genome-wide analysis were typically resulted as positive trisomy 8 with a likely maternal mosaic comment. Samples requested for traditional analysis were typically resulted as non-reportable and accompanied by a proactive call to the provider to communicate the maternal mT8 data. The sheer strength (greatly elevated Z-score) of the sequencing signal for a suspected maternal autosomal trisomy may artificially depress Z-scores of other autosomes, precluding further aneuploidy interpretation in traditional analysis samples.

The average gestational age at the time of screening for this cohort was 13 weeks 2 days. The maternal age of this cohort ranged from 20.5 years to 43.2 years, with an average of 32.3 years. In 40% of cases (n=13), no high risk indication was reported, followed closely by those at increased risk due to advanced maternal age (n=12, 36%). Having no reported high-risk indication may suggest that these patients were not at an increased risk of aneuploidy and were undergoing routine prenatal screening; however, indication is not a required field on the test requisition and as such, some indications may not have been communicated to the laboratory.

Outcome data was available for approximately 32% (9/28) of individual patients. Maternal mT8 was confirmed in 44% (4/9) of cases in which diagnostic testing results on the pregnant patient and/or fetus/placenta were available for review. No affected fetuses were identified on fetal/placental testing. One patient's maternal testing showed a normal female karyotype on peripheral blood chromosome analysis. For this particular analysis, 50 metaphase cells were counted, 5 were analyzed for banding patterns, and 3 were fully karyotyped. Maternal testing was not performed for the remaining 44% (4/9) of cases for which diagnostic testing did not confirm trisomy 8 in the fetus/placenta. For all remaining cases, maternal and/or fetal testing was not performed at our laboratory and no diagnostic outcome was reported to our laboratory by the ordering provider.

4. Conclusions

This series of cases provides insight into one cfDNA laboratory's experience with suspected maternal mT8. Given that the majority of patients in which this finding was identified were pursuing screening for advanced maternal age or had no high-risk indication provided, it appears as though maternal mT8 is often an incidental finding on cfDNA screening. Although an uncommon finding, cfDNA sequencing data suspicious for this maternal finding can lead to a non-reportable screening result due to the Z-score depression of other analyzed chromosomes. In addition to its role in non-reportable results, suspected maternal mT8 on cfDNA screening may prompt maternal genetic evaluation to assess potential implications for future pregnancies. Due to tissue specificity and/or lower level mosaicism, standard cytogenetic analysis may yield normal results while an abnormal cell line for mT8 may be present but undetectable. Communication of this mT8 data to the ordering provider, even in the context of a non-reportable result, allows the clinician the opportunity to consider clinical evaluation given the association of mT8 with MDS and hematological malignancies. One group suggests evaluation for malignancy by a multidisciplinary team and increased surveillance for patients in which a maternal mT8 is identified on cfDNA screening.[7] When detected, this suspected maternal finding can provide valuable information to clinicians and their patients.

References

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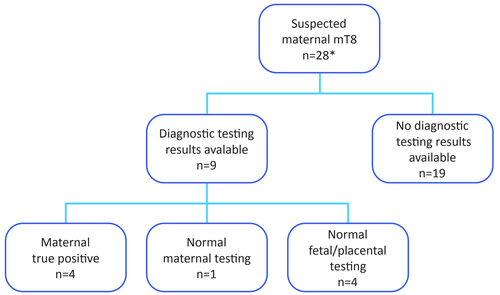
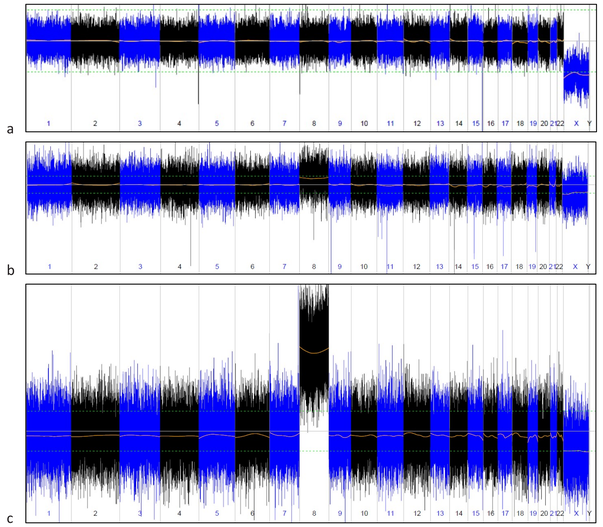
Figures

Figure 1. Breakdown of diagnostic outcomes for suspected maternal mT8 cases



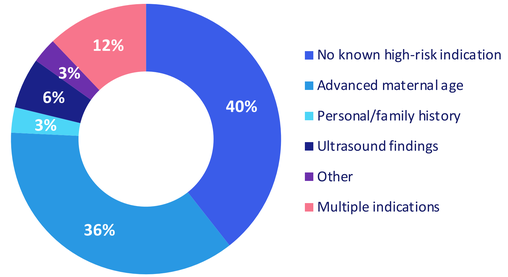
*This diagram reflects individual patients and does not include repeat samples

Figure 2. Examples of 50 kb sequencing data



These images show 50 kb traces from (**a**) a male pregnancy with a normal screening result, (**b**) a screen suggestive of fetal trisomy 8, and (**c**) a screen suggestive of maternal trisomy 8. The fetal trisomy 8 is included to show the stark contrast of the strength of the sequencing signal of chromosome 8 when compared to the maternal finding, in which the intensity artificially depresses the Z-scores of other autosomes, resulting in sequencing data below the disomy line.

Figure 3. Indications for screening



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