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Maternal fibroid impact on cfDNA screening

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1. Introduction

Cell-free DNA (cfDNA) aneuploidy screening analyzes cfDNA fragments in maternal plasma. A proportion of the circulating cfDNA is placental in origin and serves as a proxy for fetal aneuploidy status. As the remaining cfDNA originates from maternal tissue, identification of unexpected maternal findings is possible. Maternal fibroids, similar to other maternal and placental tissues, may shed cells and contribute cfDNA fragments to maternal plasma. Almost one half of fibroids have been documented to have abnormal chromosome complements which may confound fetal aneuploidy screening.[1-3] Here we investigate cfDNA data and results from 57 unique patients. with known fibroids.

2. Methods

Samples submitted to Sequenom, a subsidiary of Labcorp, for MaterniT®21 PLUS or MaterniT®GENOME testing between Jan 2016 - Aug 2021 with confirmed fibroids per clinician reporting were included. Diagnostic testing information was elicited from the clinical provider or via diagnostic samples submitted Labcorp. Genome wide data, which is available on all samples regardless of ordered test type, was reviewed for detected abnormalities.

3. Results

57 patients with known fibroids were identified and the sequencing data reviewed (**Figure 1**). The majority of samples (n=35, 61%) in this cohort resulted in a non-reportable cfDNA result and 19 (33%) resulted in a positive result. 90% (n=17) of positive results were positive for findings outside of traditional cfDNA screening with 7q deletions being the most common finding reported (n=5). Pre or postnatal diagnosis was performed in 18 pregnancies, 15/18 with positive cfDNA results and 3/18 with non-reportable results. 89% (n=16) had normal diagnostics, one case was confirmed concordant for trisomy 21, and one case of monosomy X (non-reportable by cfDNA).

In all samples (n=57) cfDNA sequencing data was reviewed for detected copy number variants (CNVs) and aneuploidies. CNVs were detected on all autosomes except chromosome 20 and most frequently observed on chromosomes 1, 7, and 3, respectively (**Figure 2 and 3**). Deletions (79%) were more commonly observed than duplications and the mean CNV size was 41.7Mb (median 33.15Mb). Trisomy 12 and 4 were the most frequently observed aneuploidies (**Table 1**). The mean number of abnormalities detected per sample was 3 (range 0-12).

4. Conclusion

As the placenta and maternal tissues contribute cfDNA fragments to plasma, it is not unexpected that a fibroid, dependent on maternal and fibroid physiology, could also contribute and potentially confound fetal aneuploidy screening (depending on individual fibroid cytogenetics). Frequent CNVs and aneuploidies reported in fibroid cytogenetic literature are consistent with observed CNVs detected by cfDNA.[1,2] This coupled with the largely normal fetal diagnostic testing, when available, supports fibroid cfDNA contribution as the likely biological explanation for this subset of false positive and non-reportable results. Upon receipt of a non-reportable or positive cfDNA result in a patient with fibroids, fibroid interference should be considered in the differential.

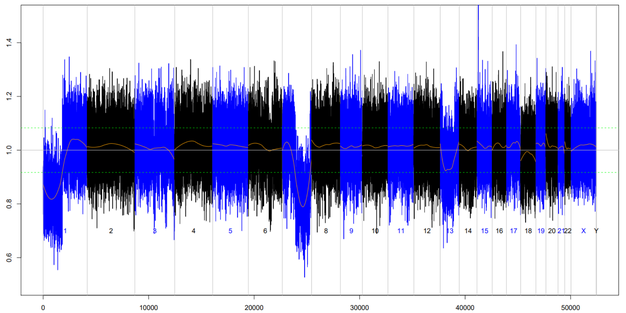
Importantly, fibroids are not a contraindication to cfDNA screening and are relatively common in the obstetrical population. This retrospectively ascertained cohort is likely enriched for non-reportables and positives; as fibroid status is not on test requisitions nor routinely reported by ordering providers.

5. Impact Statement

Maternal fibroids can be associated with abnormal sequencing data and may confound fetal aneuploidy screening. Close communication with the performing laboratory and additional counseling considerations may be important for patients with known fibroids and positive or non-reportable cfDNA.

Tables + Figures

Figure 1. Genome-wide cfDNA profile view of patient with uterine fibroid



Genome-wide cfDNA data picture above for a patient with known uterine fibroid (measuring 8cmx7cm). Sequence data is represented by the orange line normalized to 1.0. Underrepresentation is apparent at 1p, 7q, and 13q.

Figure 2. Frequency of CNVs by chromosome

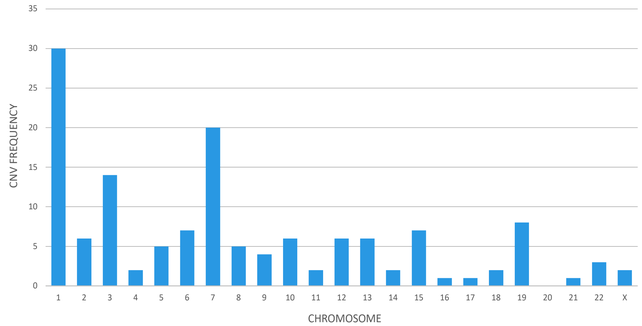
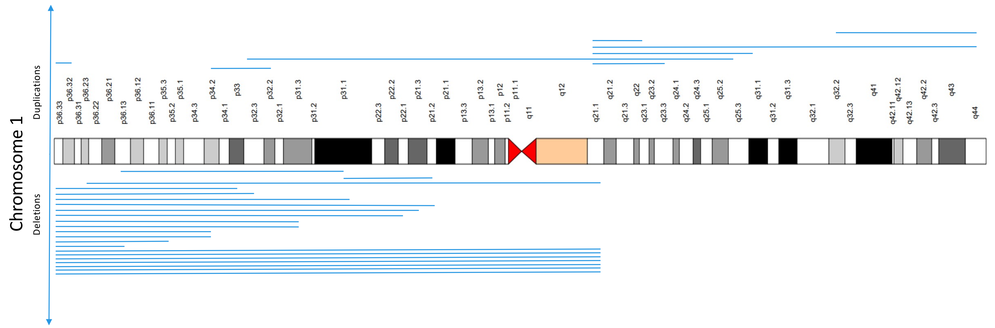


Table 1. Observed monosomies and trisomies in cfDNA samples with known fibroids

Aneuploidy	Chromosome
Monosomy	13, 14, 15, 18, 21
Trisomy	4, 5, 12, 21

Figure 3. Chromosome 1 CNVs detected by cfDNA in patients with known fibroids



Pictured is an ideogram of chromosome 1 overlaid with CNVs detected in cfDNA sequencing. Detected deletions (under) and duplications (above) are represented by the blue lines.

References

1. Ordulu Z. Fibroids: Genotype and Phenotype. *Clin Obstet Gynecol*. 2016 Mar;59(1):25-9.
2. Mehine M, et al. Integrated data analysis reveals uterine leiomyoma subtypes with distinct driver pathways and biomarkers. *Proc Natl Acad Sci U S A*. 2016 Feb 2;113(5):1315-20.
3. Dharajiya NG, et al. Uterine leiomyoma confounding a noninvasive prenatal test result. *Prenat Diagn*. 2015 Oct;35(10):990-3.

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