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The disappearing act: diminishing Y chromosome cfDNA contribution in vanished twin pregnancies

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1. Introduction

In non-invasive prenatal screening (NIPS) via cell-free DNA (cfDNA), demise of a male co-twin may lead to discordant fetal sex prediction due to persistent chromosome Y contribution but a surviving female fetus. Despite this well-known limitation in fetal sex prediction on NIPS, the timing of detection and clearance rate of chromosome Y cfDNA in vanished twin pregnancies has not been well described. Here chromosome Y contribution between serial NIPS samples is examined in 49 vanished twin pregnancies with surviving female fetuses as reported by ultrasound.

2. Methods

Maternal blood samples were submitted to Sequenom, a Labcorp subsidiary, for NIPS. Fetal fraction (FF) calculation is described in Kim et al[1]. Chromosome Y fraction (YFF) is the proportion of the sample with cfDNA fragments mapping to unique regions of the Y chromosome. Sufficient chromosome Y detection is required for male sex reporting. Cases were identified via retrospective internal database search for reported fetal sex discrepancies between March 2015 and January 2022. Included cases had a vanished twin reported by the clinician, discordant fetal sex of the surviving fetus (male by NIPS, female by ultrasound), and submitted a repeat NIPS specimen.

3. Results

For the 49 included patients with a known vanished twin and discrepant predicted male fetal sex on NIPS, the average gestational age (GA) at initial screening was 11.7 weeks with repeat sampling 3.4 – 20.9 weeks later (mean & median: 9.6 weeks). The average FF and YFF at initial sampling were 9.9% and 2.3%, respectively, and 12.2% and 0.5% at resampling. On repeat sampling YFF decreased in 96% of cases but was still detectable up to 14 weeks later in one patient. In 18% of redraw samples (n=9) there was still sufficient Y contribution to meet criteria for male fetal sex prediction despite repeat sampling occurring on average 7.5 weeks after the initial draw. The average decrease in YFF was 0.2% per week.

4. Conclusion

cfDNA contribution from the vanished twin is variable and depends on multiple factors: timing of the demise, reabsorption rates, maternal physiology. As this was a retrospective analysis, exact details about vanished twin timing was varied or unknown for most cases. Many cases reported multiple embryo transfer or second empty sac noted on early ultrasound which would indicate co-twin demise at an early GA. However, contribution of Y chromosome was still present up to 14 weeks post initial sampling. Pre-test NIPS counseling in these pregnancies should include potential for result discrepancy along with importance of ultrasound for fetal sex confirmation. In the absence of other fetal concerns, repeat NIPS sampling for discrepant fetal sex at a later GA may be a reasonable first step in the context of a known vanished twin. The average change in YFF/week may guide time to resampling. Comparison of YFF to FF may be helpful in sex discrepant cases, particularly when early ultrasound data is limited.

References

1. Kim S, Hannum G, Geis J, et al. Determination of fetal DNA fraction from the plasma of pregnant women using sequence read counts. *Prenat Diagn*. 2015;35(8):810-815.

Tables + Figures

Figure 1. Compares the total FF in the initial sample against the YFF, which is the percentage of the sample with Y chromosome present. In a sample with a singleton male fetus, typically the two fractions are approximately the same (i.e. if FF is 10%, YFF should be present in ~10% of the sample). In our cohort however, the YFF is markedly lower than expected relative to the sample's total FF.

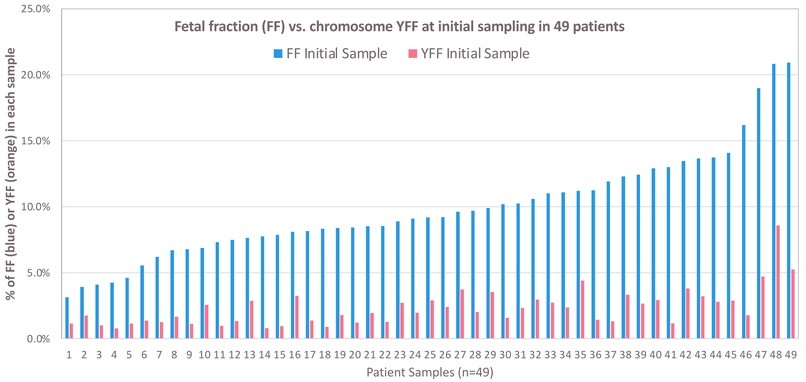
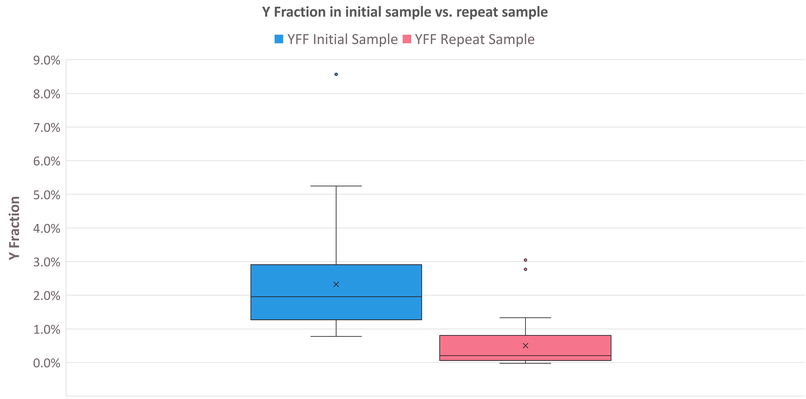


Figure 2. Compares the YFF between patients' initial and repeat samples, illustrating that over time the cfDNA from the Y chromosome decreases in pregnancies with a presumed male twin demise and surviving female fetus.



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