Implications of fetoplacental mosaicism on cell-free DNA testing for sex chromosome aneuploidies

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Objective

Cell free DNA (cfDNA) testing can screen for homogeneous sex chromosome aneuploidies (SCAs). The unique genetics of sex chromosomes, which may generate mosaic cell lines, has significant implications on the cfDNA test performance and management. The aims of this study were to predict the false positive (FPR) and false negative rates (FNR) by cfDNA testing consequent to feto-placental mosaicism for any SCAs and to predict the positive (PPV) and negative predictive values (NPV) of both high and low risk results.

Methods

Retrospective analysis of a chorionic villus sample (CVS) database including serial karyotype results of cytotrophoblast, mesenchyme and amniocytes of samples showing a placental mosaicism. Cases with a SCA cell line identified in at least one placental layer were included. Predictions of cfDNA testing performance were based on cytotrophoblast karyotype results. The percentage of each cell line in the cytotrophoblast was transformed into ‘dosage equivalent’ mimicking the quantitative counting approach of cfDNA.

Results

The cfDNA SCA FPR consequent to type 1/3 confined placental mosaicism (CPM) is predicted to be 0.05%. Other phenomena (maternal mosaicism or vanishing twin) can likely justify the published increased FPR for SCAs. The FNR is very low for all non-mosaic SCAs (0-5.7%); it is high for mosaic 45,X with normal ultrasound (70%). The predicted PPV based on amnio results is very high for most SCAs (94.4% for 47,XYY, 99.4% for 45,X cases with abnormal ultrasound); it is much lower for 45,X without ultrasound anomalies. A 45,X high risk result with normal ultrasound can reflect placental 45,X mosaicism in 50% of cases, thus requiring a confirmatory amniocentesis. It may also reflect a mosaic condition or a discordant abnormality on amniocytes in 18% of cases. The NPV for all SCAs is 99.9%.

Conclusion

A positive cfDNA 45,X result should be interpreted and managed in the content of the ultrasound evaluation: if a cystic hygroma or an increased NT is detected, a confirmatory CVS may be considered because the positive cfDNA result most likely reflects a non-mosaic 45,X karyotype in the placenta; if the ultrasound is normal, an amniocentesis will better characterize the cytogenetic composition of the fetus. For the remaining SCAs, a confirmatory CVS could also be a reliable option for patients who require an early diagnosis even in the absence of ultrasound findings, although amniocentesis still better reflects the fetal chromosomal complement. The high NPV means that cfDNA is a good tool at ruling out SCA.