

Case studies of fetal mosaicisms detected by non-invasive prenatal testing

Dear Editor,

The American College of Medical Genetics and Genomics recommended that all pregnant women be offered non-invasive prenatal testing (NIPT) regardless of the patient's risk profile.¹ With increasing NIPT uptake, encounters with genetic conditions other than the 3 common fetal trisomies are becoming prevalent. We report 2 cases of fetal mosaicisms for chromosomes 13 and 22, respectively.

Case 1. The patient was 37 years old and opted for NIPT at 12 weeks (w). Cell-free DNA from maternal plasma was extracted for subsequent low-pass whole genome sequencing. Results showed high risk for trisomy 13, while Y-chromosomal sequences were detected, indicating a male fetus. Fetal fraction was 10.7%. Amniocentesis was performed at 16w, and karyotype showed mosaic 47,XY,+13[3]/46,XY[36] (Fig.1A). Trisomy 13 mosaicism was diagnosed with 7.7% abnormal cells. She was referred for genetic counselling (GC) and extensively counselled that the fetus is at increased risk of systemic structural abnormality and intellectual disability. After GC and fetal ultrasound scan, the patient decided to proceed with termination of pregnancy (TOP) at 19w.

Case 2. The patient was 40 years old and an early scan showed no obvious structural abnormality. At 12w, she opted for NIPT and the blood was processed in the same way as in Case 1. NIPT results showed high risk for trisomy 22, and no Y-chromosomal sequences were detected, indicating a female fetus. Fetal fraction was 11.3%. Amniocentesis was performed at 15w, and karyotype showed mosaic 47,XY,+22[3]/46,XX[12] (Fig. 1B). Low-level trisomy 22 mosaicism was diagnosed with 20.0% abnormal cells. She was referred for GC and counselled on the fetal risk of hemihypertrophy, cardiac defects and development issues. Patient decided to wait for anomaly scans to screen for structural defects before proceeding with TOP. Fetal ultrasonographies at 17–19w showed a growth-restricted fetus with all parameters <1%. There was no obvious structural abnormality seen at that stage. A repeat ultrasonography done at 22w confirmed a severely growth-restricted fetus. The patient underwent medical TOP at 23w.

Both patients were referred for GC when the diagnosis was made. For case 1, she was seen by a genetic

counsellor at 18w. At that time she was counselled on the karyotype results and was given an option of waiting for fetal anomaly scan to screen for any structural abnormality. She was also informed that the presence of normal structures does not exclude the possibility of the issues and the couple opted for TOP.

Case 2 was seen by the geneticist at 17w. During GC, she was counselled on the severity range of mosaic trisomy 22 from normal and asymptomatic to phenotype with structural differences. She was also given the option of TOP versus waiting for fetal anomaly scan to screen for structural differences before deciding on TOP. The couple was also counselled on the postnatal evaluation and monitoring for the baby should they decide on continuing with the pregnancy. She decided to proceed with ultrasound scan monitoring before deciding. She had serial growth scans which showed that the fetus was growth restricted. An ultrasound scan at 22w showed that the fetus was severely growth restricted. Given the poor prognosis, the couple decided to proceed with TOP.

Both cases were referred for Women's Emotional Health Service upon diagnosis as well as after TOP for emotional and grief support.

In this report, we described 2 cases where low-level mosaicism of trisomy 13 and trisomy 22 were detected by NIPT. Amniocenteses were performed for both cases where low level 7.7% trisomy 13 and 20.0% trisomy 22 mosaicisms were found, respectively. Chromosome mosaicism is defined as having more than one cell population coexisting within the same tissue, i.e. one cell population has a normal karyotype and the other has an abnormal karyotype. It is generally recognised that phenotype will be affected if the proportion of abnormal cells exceeds 20%. However, the proportion of abnormal cells can be grossly over- or under-estimated as it depends on sampling, cell growth during culture, and type of cells that were harvested for karyotyping. It is therefore challenging to predict the severity of the phenotype based on the percentages of the abnormal cell population. Detailed fetal ultrasonography will be of importance to confirm the presence or absence of morphological abnormalities in order to estimate the phenotype. In these 2 cases, ultrasonography showed no obvious structural abnormality except severe growth restriction

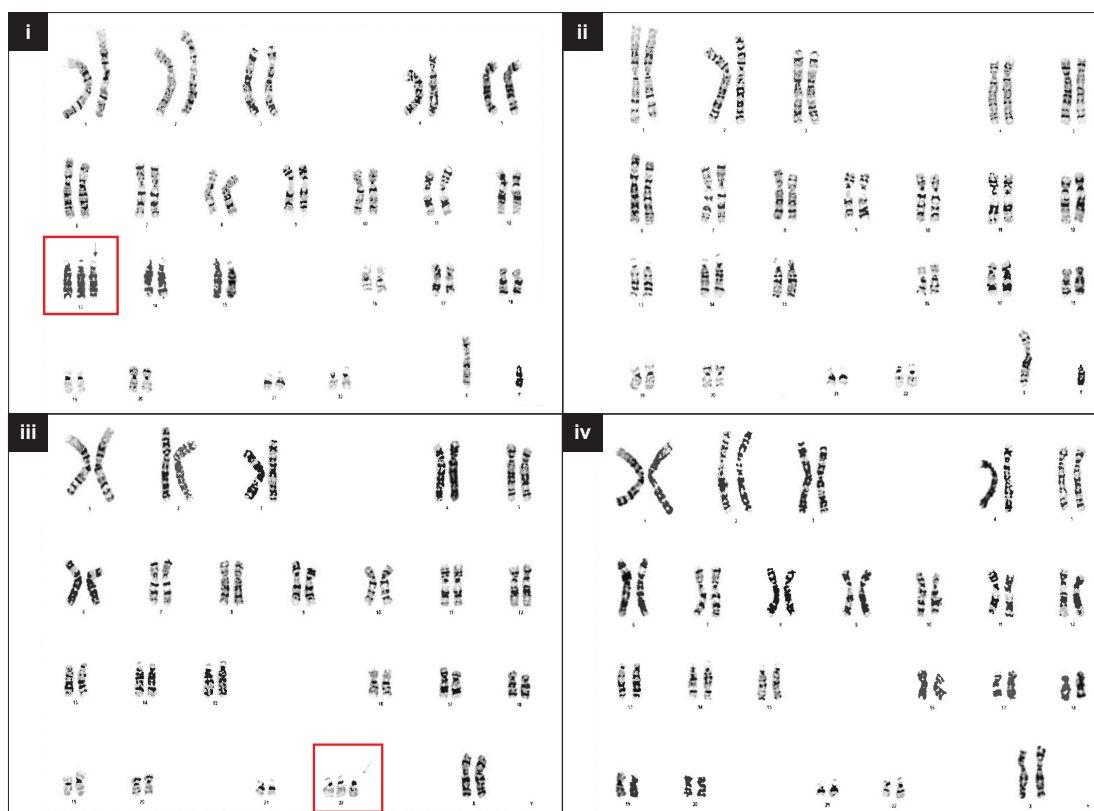


Fig. 1. The karyotypes of the amniotic fluid cultures performed for Cases 1 and 2. (A) In Case 1, cytogenetics analysis shows the presence of two cell lines with (i) trisomy 13, and (ii) normal diploid cell line. (B) In Case 2, two cell lines with (iii) trisomy 22, and (iv) normal diploid cell line were present. The karyotypes of Cases 1 and 2 are 47,XY,+13[3]/46,XY[36] and 47,XY,+22[3]/46,XX[12], respectively.

for Case 2 with trisomy 22 mosaicism as the pregnancy progresses. In trisomy 22 cases, fetuses with low-level chromosome mosaicism confined to the placenta (i.e. confined placental mosaicisms), have been reported to be compatible with life. However, mosaicism at amniocentesis and in liveborn children are rarely reported. One of these studies described low-level trisomy 22 mosaicism at amniocentesis in a pregnancy with a favourable outcome.² Trisomy 22 has been reported to be associated with normal live-born babies with low-level mosaicism of 5–30%.^{3–5} Therefore, the affected couple decided to continue the pregnancy with close ultrasound monitoring. Unfortunately for Case 2, at 22w, severe growth restriction was observed in ultrasound and the pregnancy was terminated, given the poor prognosis.

As methodologies and algorithms improve, an increasing number of cases with low-level mosaicisms can be detected by NIPT. In pretest counselling, the

patient should be informed that the detection rate of NIPT is higher than that of maternal serum screening. This includes the possibility of detecting low-level mosaicisms that will require invasive prenatal diagnosis. In addition, as NIPT analyses the cell-free fetal DNA that originates from the placenta rather than the fetus, false positives can occur in the presence of confined placental mosaicisms. To exclude false positive results, confirmatory invasive prenatal diagnostic tests using amniotic fluid and not chorionic villus sampling should be performed. As amniocentesis is performed after 15w, this will result in further delay of confirmatory diagnosis. The availability of GC is therefore of utmost importance before the healthcare provider offers NIPT. In addition, NIPT results must be interpreted in the context of the patient's clinical data and family history, so that follow-up testing or close monitoring via ultrasonography can be recommended.

REFERENCES

1. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. *Genet Med* 2016;18:1056-65.
 2. Zhang Z, Cao D, Xu Z, et al. Prenatal diagnosis of low-level trisomy 22 mosaicism with a favorable outcome. *Taiwan J Obstet Gynecol* 2021;60:380-1.
 3. Crowe CA, Schwartz S, Black CJ, et al. Mosaic trisomy 22: a case presentation and literature review of trisomy 22 phenotypes. *Am J Med Genet* 1997;71:406-13.
 4. Thomas S, Parker M, Tan J, et al. Ocular manifestations of mosaic trisomy 22: a case report and review of the literature. *Ophthalmic Genet* 2004;25:53-6.
 5. Leclercq S, Baron X, Jacquemont ML, et al. Mosaic trisomy 22: five new cases with variable outcomes. Implications for genetic counselling and clinical management. *Prenat Diagn* 2010;30:168-72.
- Arundhati Gosavi ¹*MBBS*,
 Nora Izzati Hj Ali Mashod ²*BHSci*,
 Jocelyn Ziqi Quek ²*BSc*, Sarah Aung ²*BSc*,
 Stephie Siew Fong Chin ²*BSc*, Biswas Arijit ¹*FRCOG*,
 Sherry Sze Yee Ho ²*PhD*
- ¹Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
²iGene Laboratory Pte Ltd, Singapore
- Correspondence: Dr Sherry Sze Yee Ho, iGene Laboratory Pte Ltd, Singapore,
 1 Science Park Road, #04-10, Science Park, The Capricorn, Singapore 117528.
 Email: sherry.ho@inex.sg