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Multiple deletions in chromosome 13 mediated by chromothripsis: A case report

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Introduction

Chromothripsis has been described in both human cancers and in congenital disorders and has been defined as the formation of clustered DNA rearrangements through a singular, cataclysmic event, resulting in a large number of rearranged fragments interspersed with widespread losses of sequence fragments. Several mechanisms have been proposed. These mechanisms have been identified in the field of human reproduction as causal factors for reproductive failures and chromosomal abnormalities.

Case report

A 22-year-old woman was referred for prenatal diagnosis due to abnormal maternal serum Quad screen positive for trisomy 18 and an abnormal fetal ultrasound with multiple congenital anomalies including holoprosencephaly, bilateral cleft lip, bilateral club feet, severe IUGR and possible cardiac defect. The amniotic fluid sample was received for chromosome, microarray and FISH analyses.

Results

Cytogenetic analysis of *in situ* cultured amniocytes revealed a male karyotype with an apparent distal deletion of the long arm of chromosome 13 (Figure 1). FISH showed no aneuploidy for chromosomes X, Y, 13, 18 or 21. SNP microarray (Affymetrix Cytoscan HD platform, which uses 2,029,441 nonpolymorphic copy number probes and 743,130 SNP probes for LOH/AOH analysis and relationship assessment) analysis has detected a complex series of interstitial deletions on chromosome 13 (Figure 2). The clinical phenotype of 13q deletions vary with size of the deletion and gene content. Some of the most common clinical features include moderate-severe intellectual disability, growth delay, congenital anomalies and dysmorphic features.

Discussion

Recent studies suggest that chromothripsis is not restricted to cancer. Chromothripsis could occur in human germlines and during early embryonic development. There are reports of constitutional chromothripsis associated with intellectual disability. Chromothripsis leads to complex genomic structural rearrangements, during this process, some of the fragments may be lost, while duplications are almost absent. Multiple copy number losses localized to chromosome 13 suggest that these deletions likely arose by a complex multi-break rearrangement mediated by chromothripsis.

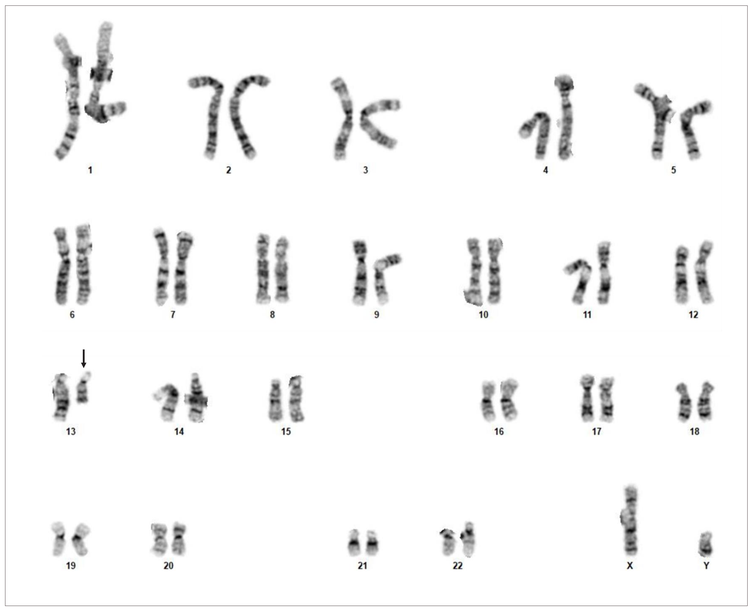

Figure 1. 46,XY,inv(9)(p12q13),del(13)(q22.1).

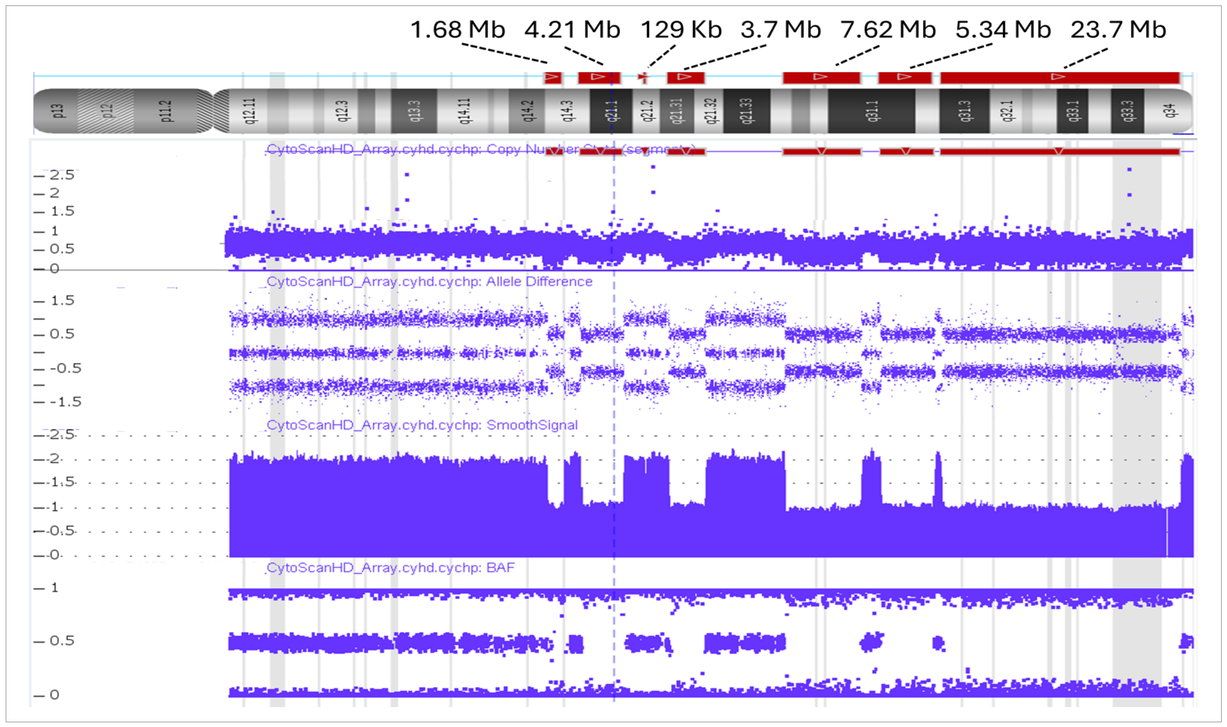

Figure 2. A male fetus with pathogenic complex series of deletions on chromosome 13. The total deleted segments are 46.38 Mb within a 64 Mb genomic region and includes numerous OMIM genes.

References

1. Pellestor F, Gatinois V. Chromoanasynthesis: another way for the formation of complex chromosomal abnormalities in human reproduction. *Hum Reprod*. 2018;33:1381-1387.
2. Budrewicz J, Chavez SL. Insights into embryonic chromosomal instability: mechanisms of DNA elimination during mammalian preimplantation development. *Front Cell Dev Biol.* 2024;12:1344092.
3. Korbel JO, Campbell PJ. Criteria for inference of chromothripsis in cancer genomes. Cell. 2013;152:1226-1236.
4. Nazaryan-Petersen L et al, Chromothripsis and DNA Repair Disorders. J Clin Med. 2020;9:613.

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