Molecular and Cytogenetic Characterization of a Fetus with Mosaic Ring Chromosome 13: A Very Rare Case

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The major mechanism for ring chromosome formation is thought to result from breakage and reunion at the breakpoints on the long and short arms of a chromosome. This fusion event can produce terminal arm inversions, deletions, and duplications that determine the resulting phenotype.[1] Ring chromosome 13 is relatively uncommon, with an estimated incidence of 1/58,000 live births. Clinical severity of ring chromosome 13 syndrome is broad and influenced by the stability of the ring as well as the extent of the deletions and/or duplications along chromosome 13.[2] Prenatal diagnosis of ring chromosome 13 is very rare. Here, we present a prenatal case with molecular cytogenetic characterization of mosaic ring chromosome 13 syndrome in a fetus with multiple abnormal ultrasound findings.

A 34-year-old woman (gravida 3, para 0) underwent cordocentesis at 24 weeks' gestation because of ultrasound abnormalities and a Down syndrome risk of 1/379 derived from second-trimester maternal serum screening. Ultrasound examination revealed a single fetus with a normal amount of amniotic fluid but with multiple abnormalities including mild intrauterine growth retardation (biparietal diameter, head circumference, and femur length consistent with 22 weeks' gestation), unclear fetal intracranial structure (likely interlinked bilateral lateral ventricles of the brain), 7.9 mm fetal neck soft-tissue thickness, 3.9 mm ventricular septal defect, and 4.0 mm pericardial effusion. Magnetic resonance imaging discovered a shortage of cavum septum pellucidum, interlinked bilateral lateral ventricles of the brain, posterior horn of the left and right ventricles were 9.5 mm/9.3 mm, small cerebellar volume, normal cerebellar vermis, unclear commissura optica, and small right eyeball. Cord blood lymphocyte culture revealed a karyotype of 46, XY, r (13) or 45, XY, −13 in 114 or 3 cells. At the same time, microarray-based comparative genomic hybridization (aCGH) on uncultured umbilical cord blood further clarified that the composition of the ring chromosome 13 included a 23.46 Mb deletion at 13q31.3q34 from 91,625,947 bp to 115,089,535 bp and 72.08 Mb duplication at 13q12.11q31.3 from 19,502,395 bp to 91,586,354 bp. Ring chromosome 13 was designated as r (13) (p11q31.3). Metaphase fluorescence *in situ* hybridization (FISH) analysis on cultured lymphocytes showed the presence of the pericentromeric 13q14.1-specific probe signal (green spectrum) in the cell with ring chromosome 13. The parental karyotypes were normal, and there was no reported family history of chromosomal abnormalities or congenital malformations. Pregnancy history was negative for exposure to teratogenic drugs, diabetes mellitus, or any other illnesses during the pregnancy. The first two pregnancies were induced abortion in early pregnancy. The parents elected to terminate the pregnancy at 26 weeks' gestation, and a 707 g male fetus was delivered with facial dysmorphisms including small mandible, thin lips, and right microphthalmia. Bilateral absent thumb and polydactylism (first finger at right hand) were also noted. Autopsy revealed bilateral septum dysplasia, small amounts of pleural effusion, and pericardial effusion.

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The most common formation of ring chromosomes involves breakage in both arms of a chromosome, resulting in a loss of the distal fragments, followed by fusion of proximal broken ends. Alternatively, some ring chromosome formations are complex rearrangements leading to concurrent deletion and contiguous duplication such as this case. Molecular studies demonstrated that the ring included a duplicated region with a concomitant distal deletion suggesting the following mechanism: an initial Robertsonian translocation occurred between one paternal and one maternal chromosome in a trisomic cell, followed by distal breakage and deletion in both long arms of the translocation, leading to the formation of a ring chromosome. Another mechanism for the formation of inverted duplications associated with terminal deletions is a U-type exchange followed by telomere capture. Telomere healing and capture are the most well-known mechanisms to stabilize broken chromosomes.[3] In our case, the healing of the broken end may have been mediated by the ring formation. These unstable chromosomes can also lead to ring chromosome loss, producing monosomic cells, which may or may not be viable. The very low-level mosaicism for monosomy 13 (3/117) in this case supports this perspective.

Although routine cytogenetic analysis by G-banding can detect common trisomies and some structural abnormalities, it is unable to define the precise breakpoint of terminal deletions. It was evident that the ring chromosome in this case led to a partial deletion of the long arm of chromosome 13 but could not confirm whether there were duplications. Thus, high-resolution micro-aCGH was utilized to refine the breakpoint region of the ring chromosome 13 and was useful in determining the gene content within the deleted and duplicated regions. However, due to its limitations for detecting low-level mosaicism, aCGH was unable to identify the monosomy 13 cell line. The most important factor affecting the phenotype of patients with ring chromosomes is the chromosome involved in the rearrangement and the extent of the deletion or duplication of genome segments that contain crucial genes for normal development. In our case, the proband had a deletion of 23.46 Mb involving 13q32, which is considered the critical band for the most severe phenotypes in 13q deletion syndrome. 13q32 deletions result in a complex phenotype related mainly to the brain, eye, and urinary tract malformations and severe mental retardation.[4] In our case, the most striking prenatal finding was the detection of a shortage of cavum septum pellucidum, interlinked bilateral lateral ventricles of the brain, the posterior horn of the left and right ventricles were 9.5 mm/9.3 mm, small cerebellar volume, normal cerebellar vermis, unclear commissura optica, and small right eyeball. Partial trisomy 13q has been shown to have both a distinctive and common phenotype resembling that of complete trisomy 13. The fetus presented here does not show characteristic trisomy 13 major features. The published cases of partial trisomy 13q helped to delineate the variable phenotype associated with this chromosome aberration. Common phenotypic features described for partial trisomy 13q are craniofacial dysmorphism, highly arched palate, short neck, hemangioma, hexadactyly, urinary tract/kidney anomalies, umbilical/inguinal hernia, intrauterine growth retardation, and oligohydramnios.[5] This present case involves trisomy for a large segment of proximal 13q (13q12.11 → q31.3). The proband shares the features of polydactyly, thin lips, and intrauterine growth retardation with the previously reported cases.

In summary, the utilization of both cytogenetic and microarray studies is essential for the accurate diagnosis and counseling of prenatal cases with multiple ultrasound anomalies. Since prenatal diagnosis of r (13) is very rare, our case is a meaningful supplement to define a characteristic prenatal phenotype-genotype correlation. The success and accuracy of such correlation depend on the analysis of a sufficiently large number of patients with complete phenotypic malformations and molecular description of identical chromosome aberrations.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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