

# TRISOMY 13 MOSAICISM ASSOCIATED WITH CYCLOPIA AND CYSTIC HYGROMA

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A 33-year-old, gravida 2, para 0, woman was referred to the hospital because of intrauterine fetal death at 19 weeks' gestation. Her pregnancy was uneventful until that point when ultrasonography revealed a dead fetus with cystic hygroma and a fetal biometry equivalent to 17 weeks' gestation. The pregnancy was terminated. A dead 300-g fetus with cystic hygroma, holoprosencephaly (HPE), a single orbit and cyclopia was delivered (Figure 1). Neither facial cleft nor polydactyly was present. Postnatal cytogenetic analysis of placental tissue following long-term culture showed a 47,XY,+13[17]/46,XY[23] karyotype. Seventeen out of 40 cultured chorionic villus cells (42.5%) had an abnormal 47,XY,+13 karyotype, while 23 cells (57.5%) had a normal 46,XY karyotype. Molecular analysis of fetal and placental tissues confirmed true mosaic trisomy 13.

DNA was isolated from uncultured fetal skin and placental tissue. Quantitative fluorescence polymerase chain reaction assays and polymorphic short tandem repeat markers for chromosome 13 were used for determination of aneuploidy. Mosaic trisomy 13 was evident in fetal skin and placenta. The specimens of fetal skin and placenta showed a diallelic pattern with a dosage ratio of 1:1.26 and 1:1.31, respectively, for the chromosome 13-specific markers (Figure 2).

Complete trisomy 13 is well known to be associated with major structural abnormalities such as brachycephaly, microcephaly, HPE, Dandy-Walker complex, posterior fossa abnormalities, enlarged cisterna magna,

ventriculomegaly, neural tube defects, congenital heart defects, facial cleft, micrognathia, cystic hygroma, nuchal edema, hydrops fetalis, omphalocele, diaphragmatic hernia, urinary tract abnormalities, abnormal extremities, and polydactyly. Trisomy 13 mosaicism displays phenotypic variability, and some of the more characteristic physical findings observed in complete trisomy 13, such as HPE and omphalocele, are rarely reported in cases with trisomy 13 mosaicism [1]. In a literature review of 49 published cases with trisomy 13 mosaicism, Griffith et al [1] found only three patients with HPE [2–4] and only one with omphalocele [5]. However, congenital heart defects, facial cleft, seizures, polydactyly, micrognathia, a short neck and ear anomalies are common in patients with trisomy 13 mosaicism [1].

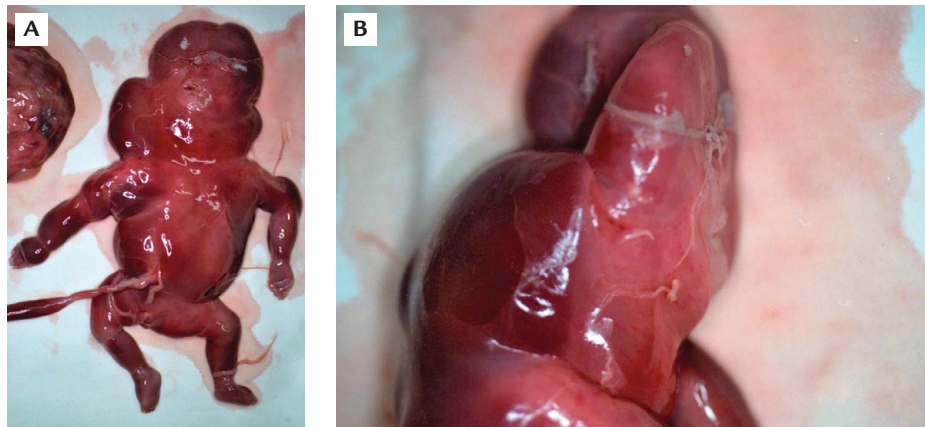
The present case is the fourth reported case of trisomy 13 mosaicism associated with HPE. Wilson and Melnyk [2] first reported mosaic translocation trisomy 13 in an infant with HPE and premaxillary agenesis, with the translocation detected in 30% of blood lymphocytes. Toledo and Wajntal [3] reported mosaic trisomy 13 in an infant with HPE, premaxillary agenesis, microcephaly, profound mental retardation and growth failure, with trisomy 13 in 15.4% of blood lymphocytes. Lorch et al [4] reported mosaic trisomy 13 in an infant with cebocephaly and a 10% mosaicism of trisomy 13. Trisomy 13 accounts for up to 75% of chromosomal abnormalities associated with HPE [6]. In a meta-analysis of 132 fetuses with prenatally detected HPE, Snijders et al [7] reported chromosomal abnormalities in 33% of the cases, including trisomy 13 ( $n=30$ ), trisomy 18 ( $n=7$ ) and other rearrangements ( $n=7$ ).

The present case is the first reported case of trisomy 13 mosaicism associated with cystic hygroma. About 75% of fetuses with cystic hygroma in the second

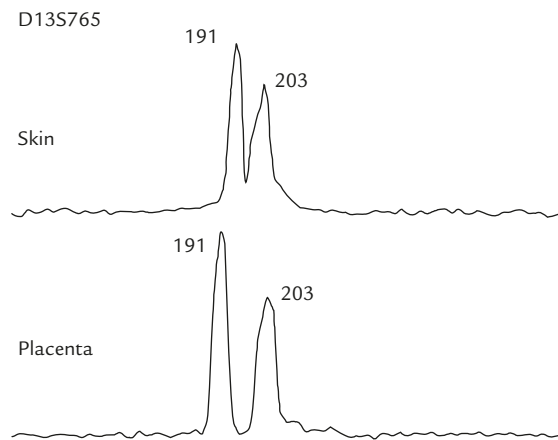


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**Figure 1.** (A, B) A malformed, macerated fetus at 19 weeks' gestation with trisomy 13 mosaicism, cyclopia, a single orbit, and cystic hygroma.



**Figure 2.** Representative electrophoretogram of quantitative fluorescence polymerase chain reaction assays for short tandem repeat markers for chromosome 13, using fetal skin and placenta. With the microsatellite marker D13S765, two peaks (191 and 203 bp) of unequal fluorescence activity with ratios of 1:1.26 and 1:1.31 were seen in the specimens of fetal skin and placenta, respectively.

trimester are associated with chromosomal abnormalities, and Turner syndrome accounts for 80% of these cases [8]. The rate of chromosomal abnormalities associated with cystic hygroma in the first trimester appears to be lower (about 50–60%), and the occurrence of autosomal trisomies appears to be more common (about 60–70%) than in the second trimester. Johnson et al [9] reported chromosomal abnormalities in 60.3% (41/68) of fetuses with first-trimester cystic hygroma, including trisomy 21 ( $n=16$ ), trisomy 18 ( $n=9$ ), trisomy 13 ( $n=2$ ), 45,X ( $n=9$ ) and other rearrangements ( $n=5$ ). Trauffer et al [10] reported chromosomal abnormalities in 48.8% (21/43) of fetuses with first-trimester cystic hygroma, including trisomy 21 ( $n=9$ ), trisomy 18 ( $n=4$ ), trisomy 13 ( $n=1$ ), Turner syndrome ( $n=4$ ) and translocations ( $n=3$ ).

Malone et al [11] reported chromosomal abnormalities in 50.8% (67/132) of fetuses with first-trimester septated cystic hygroma, including trisomy 21 ( $n=25$ ), Turner syndrome ( $n=19$ ), trisomy 18 ( $n=13$ ), trisomy 13 ( $n=6$ ), triploidy ( $n=3$ ) and mosaic deletion of chromosome 9 ( $n=1$ ). Kharrat et al [12] reported chromosomal abnormalities in 59.5% (25/42) of fetuses with first-trimester cystic hygroma, including trisomy 18 ( $n=10$ ), trisomy 13 ( $n=6$ ) and 45,X ( $n=9$ ). Graesslin et al [13] reported chromosomal abnormalities in 52.8% (38/72) of fetuses with first-trimester cystic hygroma, including trisomy 21 ( $n=14$ ), trisomy 18 ( $n=7$ ), trisomy 13 ( $n=3$ ), Turner syndrome ( $n=11$ ) and other rearrangements ( $n=3$ ). In a meta-analysis, Molina et al [14] found chromosomal abnormalities in 53.1% (139/262) of fetuses with first-trimester cystic hygroma, including trisomies 21, 18 and 13 ( $n=84$ ), Turner syndrome ( $n=42$ ) and other rearrangements ( $n=13$ ).

Counseling parents of a child with trisomy 13 mosaicism remains difficult because of the phenotypic variability associated with the condition; some patients have a typical phenotype of complete trisomy 13 with neonatal death, while others have few dysmorphic features and prolonged survival [1,15,16]. We have presented an unusual case of trisomy 13 mosaicism associated with concomitant cyclopia and cystic hygroma. Perinatal identification of concomitant HPE and cystic hygroma should prompt cytogenetic analysis to rule out chromosomal abnormalities. As demonstrated in this case, placental tissue is a valuable source of material for cytogenetic analysis of malformed fetuses following intrauterine fetal death. Quantitative fluorescence polymerase chain reaction provides a powerful tool for rapid tissue confirmation of true chromosomal mosaicism.

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