

Research Letter

## Rapid aneuploidy diagnosis of trisomy 18 by array comparative genomic hybridization using uncultured amniocytes in a pregnancy with fetal arachnoid cyst detected in late second trimester

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A 30-year-old gravida 2 para 1 (G2P1) woman was referred to the hospital at 22 weeks of gestation because of abnormal sonographic findings. The woman and her husband were non-consanguineous and healthy, and there was no family history of congenital heart or brain defects. Level II ultrasound revealed a singleton fetus with microcephaly (biparietal distance: 4.77 cm and head circumference: 18.35 cm, all less than 5th centile), rocker-bottom feet, a ventricular septal defect (VSD), and a 2.36 cm × 1.51 cm midline interhemispheric hypoechoic homogeneous lesion (Fig. 1). Prenatal magnetic resonance imaging (MRI) confirmed the diagnosis of an arachnoid cyst and hypogenesis of cerebellar vermis (Fig. 2). The corpus callosum and cerebral ventricles were normal. Amniocentesis was performed and 37 mL amniotic fluid was aspirated. About 20 mL of amniotic fluid was applied for array-comparative genomic hybridization (aCGH) using uncultured amniocytes, and 15 mL was applied for conventional cytogenetic analysis using cultured amniocytes. Within three days, bacterial artificial chromosome (BAC)-based

aCGH showed the result of trisomy 18 [arr cgh 18p11.32q23 (RP11-1150C18 → RP11-87C15) × 3; Fig. 3A). Fluorescence *in situ* hybridization (FISH) analysis of the cultured interphase amniocytes using a combination of BAC probes RP11-29G21 (18q12.3) (40,213,562-40,396,293 bp; spectrum



Fig. 1. Prenatal ultrasound at 22 weeks of gestation reveals a 2.36 cm × 1.51 cm midline interhemispheric hypoechoic homogeneous lesion.

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Fig. 2. Magnetic resonance imaging (MRI) at 22 weeks of gestation shows an interhemispheric arachnoid cyst (black arrows), and hypogenesis of cerebellar vermis (white arrow) consistent with the diagnosis of Dandy-Walker variant. (A) Sagittal; (B) axial; and (C) coronal views of the MRI findings.

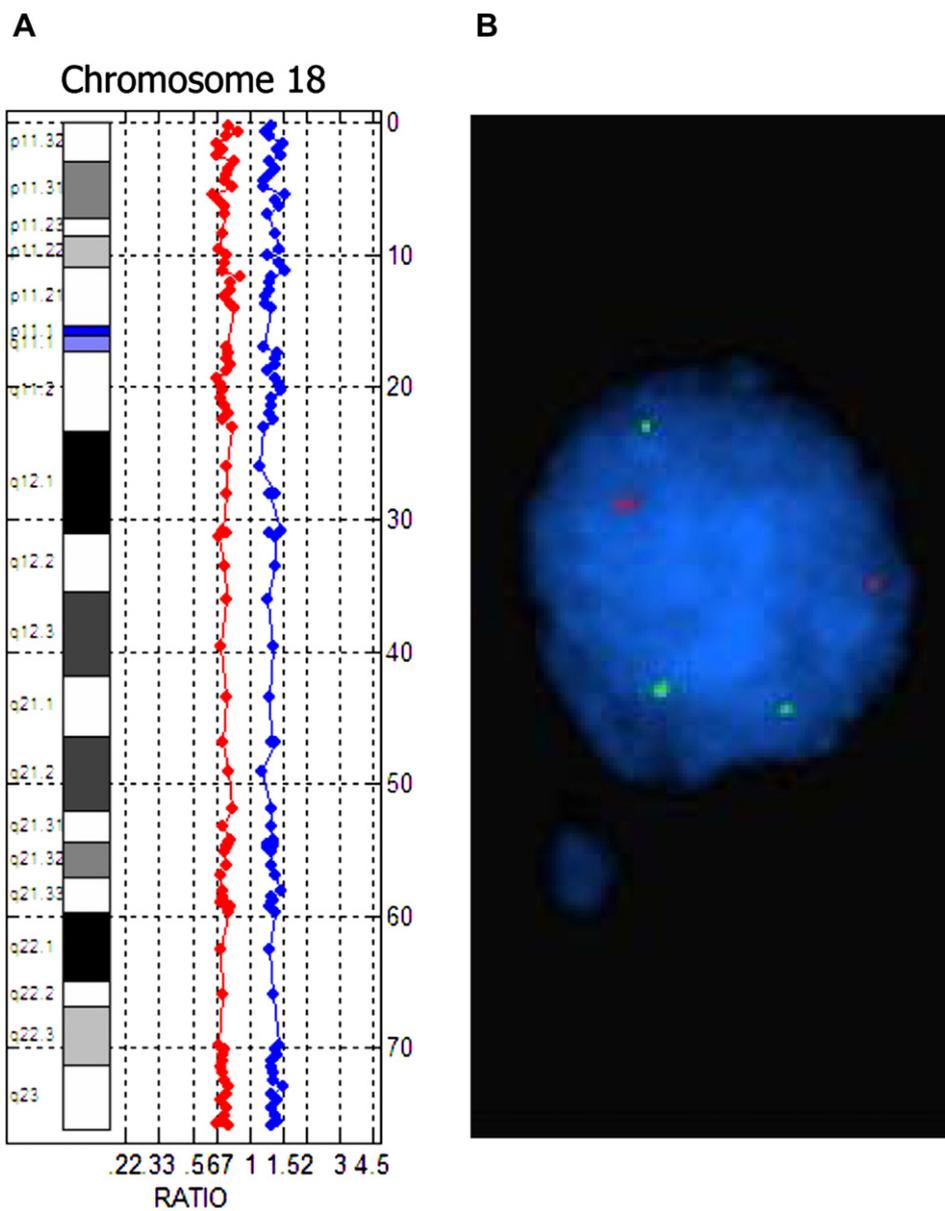


Fig. 3. (A) Bacterial artificial chromosome (BAC)-based array comparative genomic hybridization (aCGH) analysis using CMDX BAC aCGH CA3000 chips shows a duplication of chromosome 18 consistent with the diagnosis of trisomy 18; (B) Fluorescence *in situ* hybridization (FISH) analysis of interphase amniocytes using BAC probes RP11-29G21 (18q12.3; spectrum green) and RP11-98B6 (4q11-q12; spectrum red) shows three green signals and two red signals consistent with the diagnosis of trisomy 18.

green) and RP11-98B6 (4q11-q12) (52,681,899–52,856,481 bp; spectrum red) showed three green signals and two red signals consistent with the diagnosis of trisomy 18 (Fig. 3B). Eight days following amniocentesis, conventional cytogenetic analysis revealed a karyotype of 47,XY,+18. The pregnancy was terminated at 23 weeks of gestation, and a 526-g male fetus was delivered with facial dysmorphism and syndactyly of the first and second toes in the left foot and syndactyly of the third and fourth toes in the right foot. Polymorphic DNA marker analysis using quantitative fluorescent polymerase chain reaction (QF-PCR) showed that trisomy 18 in this fetus was caused by a duplication of chromosome 18 of maternal origin (Fig. 4).

We previously described prenatal diagnosis of aneuploidy by aCGH using cultured or uncultured amniocytes [1–4]. In this report, we further demonstrate that amniocentesis for genome-wide analysis using uncultured amniocytes and aCGH is a useful alternative to cordocentesis in rapid aneuploidy diagnosis in pregnancy with abnormal ultrasound findings detected in late second trimester.

Arachnoid cysts are a rare central nervous system malformation representing only 1% of all intracranial masses in newborns [5]. Prenatal ultrasound and MRI have led to the increased diagnosis of fetal arachnoid cysts mostly in the third trimester [6–8]. However, in a few cases, the diagnosis has been made in the second trimester or even in the first trimester [6,9]. Arachnoid cysts may progressively enlarge *in utero* causing ventriculomegaly and may be associated with corpus callosum dysgenesis. Prenatal MRI helps to demonstrate compression of the aqueduct, communication between the cyst and the ventricles, and corpus callosum dysgenesis.

We have presented a rare occurrence of second-trimester diagnosis of trisomy 18 in association with a midline interhemispheric fetal arachnoid cyst, microcephaly, a VSD and rocker-bottom feet. Pilu *et al* [10] first reported prenatal diagnosis of trisomy 18 at 22 weeks of gestation in a fetus

with a small arachnoid cyst in ambient cistern in association with a double-outlet right ventricle and clenched hands. Fetal arachnoid cysts can be associated with various chromosomal abnormalities. Hogge *et al* [11] reported partial trisomy 9q (9q22 → qter) and partial monosomy Xq (Xq22 → qter) in a fetus with an infratentorial arachnoid cyst. The fetus postnatally manifested a prominent nose, micrognathia, overlapping of the fingers and a thin-walled cyst compressing the right cerebellar hemisphere. Souter *et al* [12] reported a subtelomeric deletion of the distal long arm of chromosome 14, or monosomy 14q (14q32.3 → qter) in a fetus with tetralogy of Fallot, intrauterine growth restriction, and a midline intracranial arachnoid cyst. The infant postnatally manifested facial dysmorphism, inguinal hernias, tetralogy of Fallot, a midline arachnoid cyst and marked global developmental delay. Elbers and Furness [13] reported the association of triploidy with a fetus with an arachnoid cyst. Stein *et al* [14] reported prenatal diagnosis of trisomy 20 mosaicism associated with an arachnoid cyst of basal cistern. We suggest that prenatal diagnosis of arachnoid cyst, especially in association with structural abnormalities, should alert aneuploidy and prompt a cytogenetic investigation.

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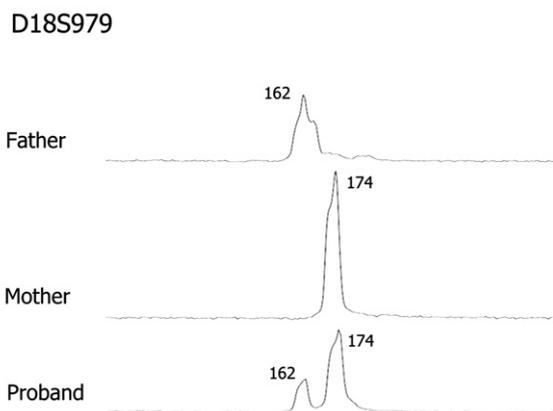


Fig. 4. Representative electrophoretogram of quantitative fluorescent polymerase chain reaction (QF-PCR) assays at short tandem repeat (STR) markers for chromosome 18. With the marker D18S979, two peaks (162 bp: 174 bp) of unequal fluorescent activity from different parental alleles (paternal: maternal) with a ratio of 1:2 in the cultured amniocytes indicates a duplication of chromosome 18 of maternal origin.

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