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Taiwanese Journal of Obstetrics & Gynecology 50 (2011) 549–553

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Research Letter

Prenatal diagnosis of mosaic trisomy 9

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Accepted 19 September 2011

A 42-year-old, gravida 5, para 2, woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. She had experienced two spontaneous abortions and had two healthy daughters. Her husband was 45 years old. There was no family history of congenital malformations. In six out of 15 separated colonies of cultured amniocytes, an

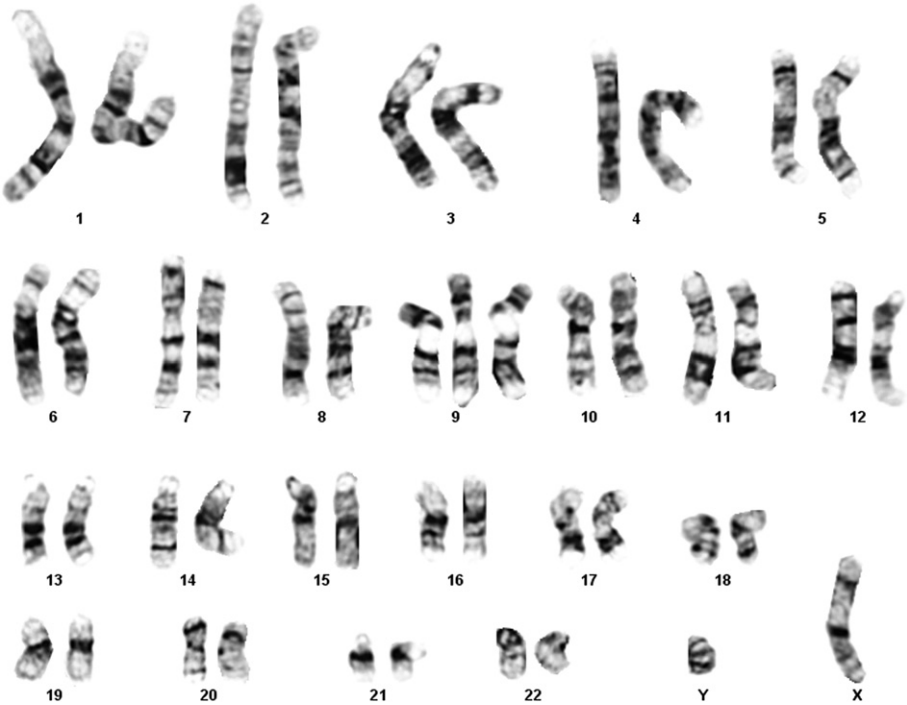

Fig. 1. A karyotype of 47,XY,+9.

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doi:10.1016/j.tjog.2011.10.031

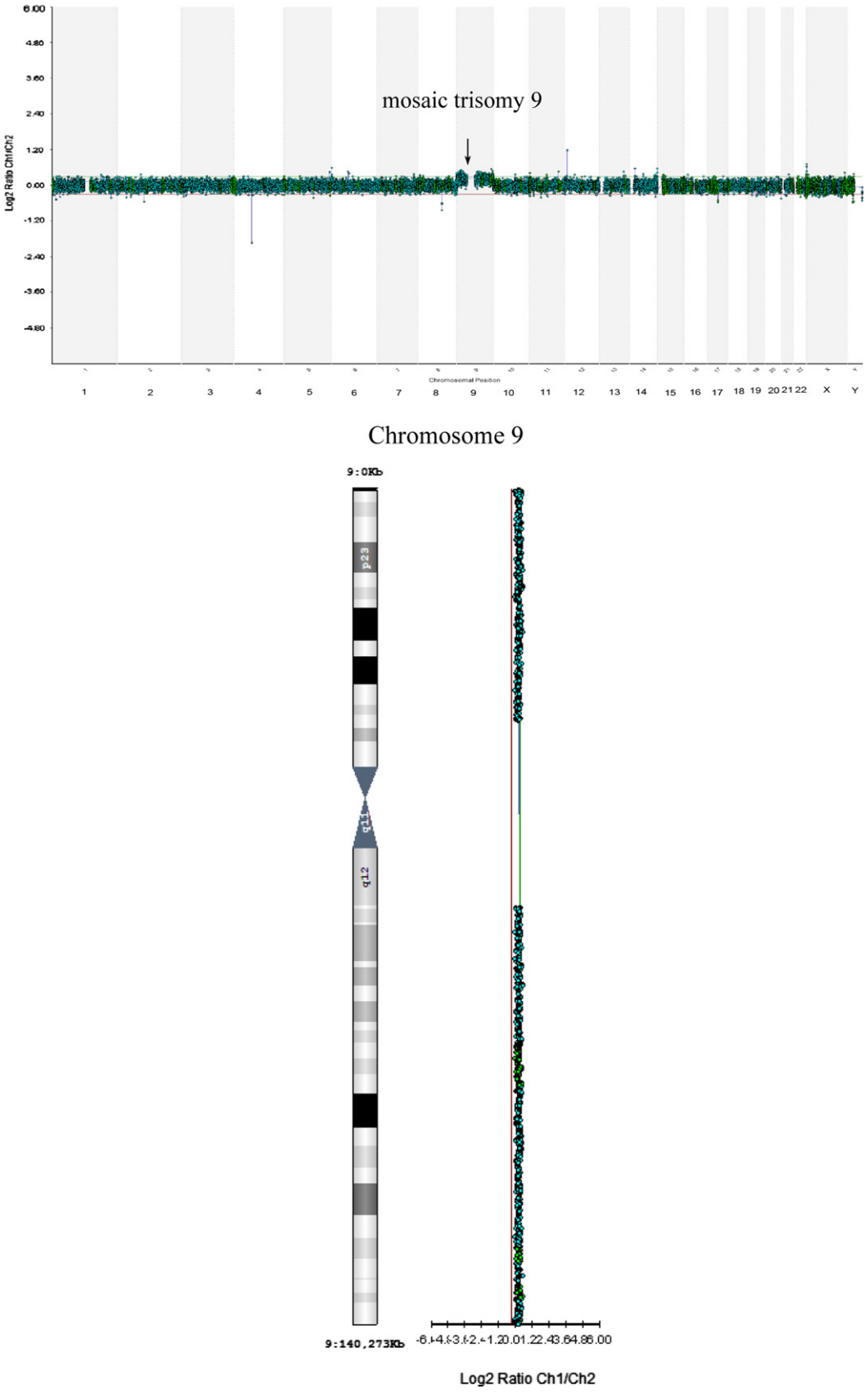

Fig. 2. Array comparative genomic hybridization analysis of uncultured amniocytes shows genomic imbalance and gene dosage increase in chromosome 9.

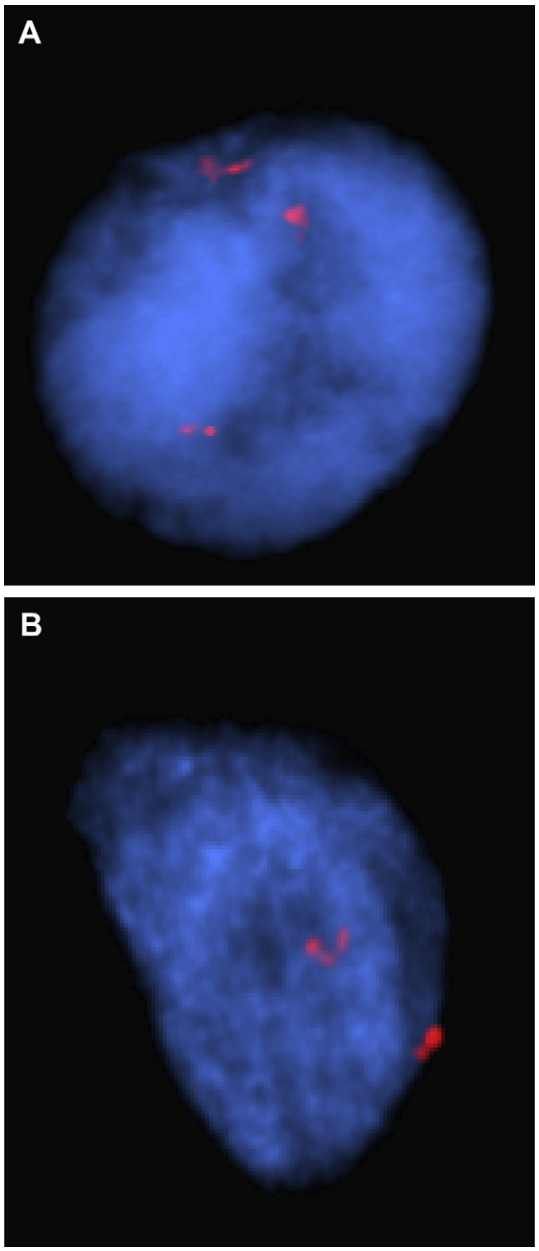

Fig. 3. Interphase fluorescence *in situ* hybridization analysis of uncultured amniocytes shows (A) three signals in a cell with trisomy 9 and (B) two signals in a cell with disomy 9, consistent with the diagnosis of mosaic trisomy 9.

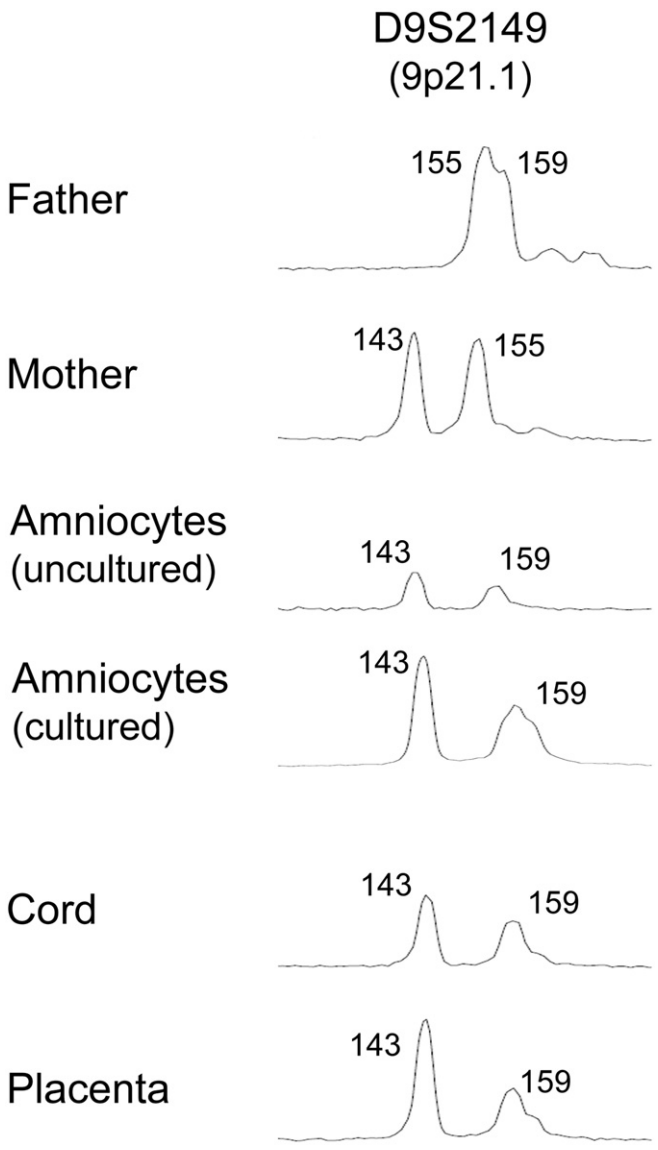

Fig. 4. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays. The marker D9S2149 (9p21.1) shows two peaks (143 bp: 159 bp; maternal: paternal) of unequal fluorescent activity from two different parental alleles in the sampling tissues with maternal:paternal dosage ratios of 1.66:1, 1.08:1, 1.19:1 and 2:1, respectively, in uncultured amniocytes, cultured amniocytes, umbilical cord and placenta.

abnormal karyotype of 47,XY,+9 was found (Fig. 1), while the other nine colonies had a karyotype of 46,XY. The cytogenetic result of amniocentesis was 47,XY,+9[6]/46,XY[9]. The parental karyotypes were normal. The woman requested a repeat amniocentesis at 20 weeks of gestation when the ultrasound revealed that the fetal biometry was equivalent to 18 weeks. Array comparative genomic hybridization (aCGH) analysis of uncultured amniocytes using oligonucleotide-based aCGH of CytoChip Oligo Array (BlueGnome, Cambridge, UK) revealed genomic imbalance and gene dosage increase in chromosome 9 (Fig. 2). Fluorescence *in situ* hybridization (FISH) analysis of uncultured interphase amniocytes using Vysis CEP 9 Alpha SpectrumOrange DNA probe (Vysis, Downers Grove, IL, USA) showed three signals in 12 out of 25 uncultured amniocytes and two signals in the remaining 13 amniocytes, indicating 48% (12/25) mosaicism for trisomy 9 (Fig. 3). Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis of uncultured amniocytes using informative microsatellite markers specific for chromosome 9 revealed a diallelic pattern with unequal biparental inheritance of chromosome 9 with a dosage ratio of 1.66:1 (maternal: paternal), indicating a maternal origin of mosaic trisomy 9 (Fig. 4). Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47,XY,+9[6]/46,XY[18]. The parents decided to terminate the pregnancy at 23 weeks of gestation. Prenatal ultrasound revealed a small-for-gestational-age fetus with fetal biometry equivalent to 21 weeks. A 482-g malformed fetus was delivered with hypertelorism, a large forehead, a bulbous nose,

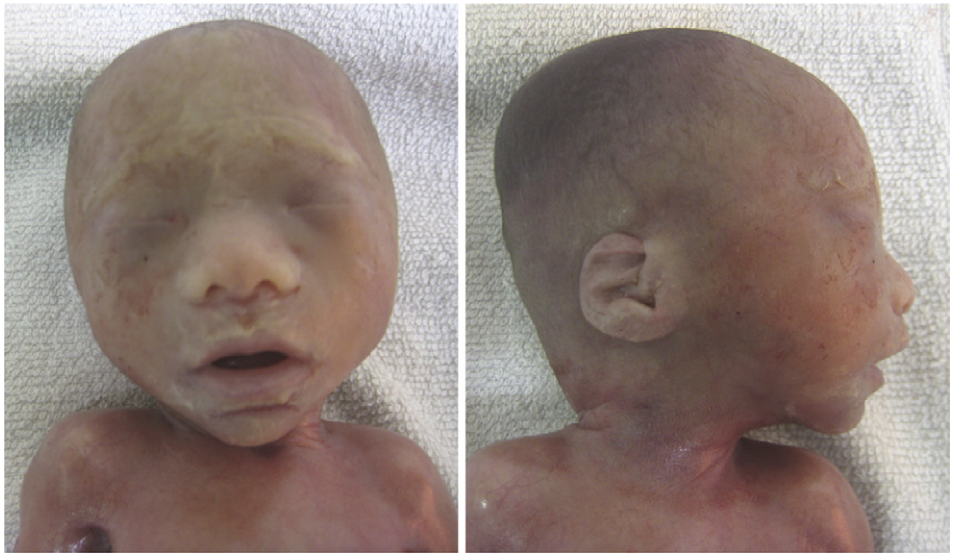

Fig. 5. The fetus at birth.

a broad nasal bridge, low-set posteriorly rotated ears, and a thin upper lip (Fig. 5). Uniparental disomy (UPD) 9 was excluded. Cytogenetic analyses of the fetal and extraembryonic tissues showed a karyotype of 47,XY+9[5]/46,XY[35] in the cord blood, a karyotype of 47,XY+9[5]/46,XY[35] in the umbilical cord, and a karyotype of 47,XY+9 (40 cells) in the placenta. The results of QF-PCR analyses of cultured amniocytes and uncultured umbilical cord were consistent with mosaic trisomy 9, and the result of QF-PCR analysis of uncultured placental tissues was consistent with trisomy 9 of maternal origin (Fig. 4).

Mosaic or non-mosaic trisomy 9 is characterized by mental retardation, growth restriction, facial dysmorphim, low-set ears, microphthalmia, a bulbous nose, a small mouth, a high-arched palate, congenital heart defects (most commonly ventricular septal defect), genitourinary anomalies (hypoplastic genitalia, cryptorchidism, cystic kidneys, or hydronephrosis), skeletal anomalies (joint dislocations or deformations), and central nervous system anomalies (hydrocephalus or Dandy-Walker malformation) [1–3]. The present case prenatally manifested intrauterine growth restriction (IUGR), but was not associated with major anomalies. In a review of 37 cases of prenatally detected mosaic trisomy 9, Chen et al. [3] found that 64.9% (24/37) of the cases were associated with phenotypic abnormalities. In a study of 12 individuals of long-term survivors with trisomy 9 mosaicism, Bruns [4] reported a mean (±standard deviation, SD) birth weight of 2228.6 g (±547.72 g) (range: 1361–3232 g) for a mean gestational age of 38 weeks. IUGR has been reported to be a prenatal ultrasound finding of mosaic trisomy 9 [5–7]. In the present case, the placenta had trisomy 9. We speculate that IUGR in the present case may be in part caused by a trisomy 9 placenta and placental dysfunction.

The interphase FISH study of uncultured amniocytes, as shown in this presentation, is an efficient method for confirmation of the status of mosaic trisomy 9 detected at amniocentesis. Chen et al. [3] previously showed that aCGH was unable to detect 18% (9/50) of mosaic trisomy 9 in the uncultured amniocytes. In this study, aCGH and QF-PCR were able to detect mosaic trisomy 9 under the circumstance of 48% (12/25) mosaic trisomy 9 in the uncultured amniocytes. The present case was not associated with UPD 9. Mosaic trisomy 9 has been reported to be associated with UPD 9, and QF-PCR provides the advantages of detecting both mosaicism and UPD.

In conclusion, mosaic trisomy 9 at amniocentesis can be associated with IUGR and trisomy 9 in the placenta. Molecular cytogenetic technologies such as interphase FISH, aCGH and QF-PCR using uncultured amniocytes are useful for rapid confirmation of high-level mosaicism for trisomy 9 detected at amniocentesis.

Acknowledgments

This work was supported by research grants NSC-97-2314-B-195-006-MY3 and NSC-99-2628-B-195-001-MY3 from the National Science Council, and MMH-E-100-04 from Mackay Memorial Hospital, Taipei, Taiwan.

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