Mosaic Trisomy 9 at Amniocentesis: Prenatal Diagnosis and Molecular Genetic Analyses

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SUMMARY

Objective: To present prenatal diagnosis and molecular genetic analyses of mosaic trisomy 9.

Materials, Methods and Results: A 35-year-old woman, gravida 3, para 1, underwent amniocentesis at 17 weeks of gestation because of her advanced maternal age. Amniocentesis revealed a karyotype of 47,XX,+9[3]/46,XX[6]. Repeat amniocentesis at 19 weeks of gestation revealed a karyotype of 47,XX,+9[6]/46,XX[19]. At 22 weeks of gestation, she was referred to a tertiary medical center for genetic counseling, and amniocentesis revealed a karyotype of 47,XX,+9[2]/46,XX[22]. Array comparative genomic hybridization analysis of uncultured amniocytes revealed no genomic imbalance in chromosome 9. However, interphase fluorescence *in situ* hybridization analysis of uncultured amniocytes showed that nine (18%) of 50 cells were trisomic for chromosome 9. Polymorphic DNA marker analyses also revealed a diallelic pattern with unequal biparental inheritance of chromosome 9 and a dosage ratio of 1:18 (paternal allele:maternal allele) in the uncultured amniocytes and a dosage ratio of 1:36 in the cultured amniocytes, indicating that the euploid cell line had maternal uniparental isodisomy for chromosome 9. Level II ultrasound demonstrated bilateral ventriculomegaly. The pregnancy was subsequently terminated, and a malformed fetus was delivered. Postnatal cytogenetic and polymorphic DNA marker analyses of the fetal and extraembryonic tissues confirmed the prenatal diagnosis.

Conclusion: Mosaic trisomy 9 carries a high risk of fetal abnormalities warranting detailed sonographic investigation of congenital malformations. Mosaic trisomy 9 can be associated with maternal uniparental disomy for chromosome 9 in euploid cell lines. Array comparative genomic hybridization is limited for the detection of low-level mosaicism. [*Taiwan J Obstet Gynecol* 2010;49(3):341–350]

Key Words: amniocentesis, mosaicism, mosaic trisomy 9, trisomy 9, uniparental disomy for chromosome 9

Introduction

Genetic counseling of mosaic trisomy at amniocentesis is difficult because of the phenotypic variability associated with the condition; some fetuses exhibit the typical phenotype, while others are normal [1–3]. Trisomy 9, mosaic or non-mosaic, is a relatively uncommon chromosomal abnormality that has characteristic phenotypic features including growth and mental retardation, dysmorphic faces with low-set malformed ears, microphthalmia, a bulbous nose and 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

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Accepted: July 7, 2010

or deformations), and central nervous system anomalies (hydrocephalus or Dandy-Walker malformation) [4–11]. Cases with mosaic trisomy 9 have been reported to be associated with maternal uniparental disomy for chromosome 9 (UPD 9) [12–14]. Here, we report the prenatal diagnosis and molecular genetic analyses of mosaic trisomy 9 with maternal isodisomy of chromosome 9 in a second-trimester fetus with ventriculomegaly and facial dysmorphism.

Materials, Methods and Results

A 35-year-old woman, gravida 3, para 1, underwent amniocentesis at 17 weeks of gestation because of her advanced maternal age. She had experienced one spontaneous abortion and had a 12-year-old healthy son. Her husband was 38 years old. Both parents were healthy, and there was no family history of congenital malformations. In three out of nine separated colonies of amniocytes, an abnormal karyotype of 47,XX,+9 was found (Figure 1), while the other six colonies had a karyotype of 46,XX. The cytogenetic result of amniocentesis was 47,XX,+9[3]/46,XX[6]. Repeat amniocentesis at 19 weeks of gestation revealed a karyotype of 47,XX,+9[6]/46,XX[19]. She was referred to Mackay Memorial Hospital for genetic counseling at 22 weeks of gestation, and amniocentesis was repeated. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47,XX,+9[2]/46,XX[22]. The parental karyotypes were normal. Array comparative genomic hybridization (aCGH) analysis of uncultured amniocytes did not manifest any genomic imbalances in chromosome 9 (Figure 2).

Fluorescence *in situ* hybridization (FISH) analysis of uncultured interphase amniocytes using TelVysion 9q SpectrumOrange DNA probe (Abbott, IL, USA) showed three signals in nine out of 50 uncultured amniocytes and two signals in the remaining 41 amniocytes, indicating low-level mosaicism for trisomy 9 (Figure 3). Quantitative fluorescent polymerase chain reaction (QF-PCR) analyses of uncultured and cultured amniocytes using informative microsatellite markers specific for chromosome 9 revealed a diallelic pattern with unequal biparental inheritance of chromosome 9 (Figure 4). The uncultured amniocytes had a dosage ratio of 1:18 (paternal allele:maternal allele), and the cultured amniocytes had a dosage ratio of 1:36. The maternal allele dosage was much greater than the paternal allele dosage, indicating that the euploid cell line contained two homologous chromosomes 9 of maternal origin and had maternal uniparental isodisomy 9. Trisomy 9 mosaicism in this case was most likely the result of a postzygotic mitotic error or less likely the result of partial trisomic zygote rescue of a meiotic II nondisjunction error of maternal origin.

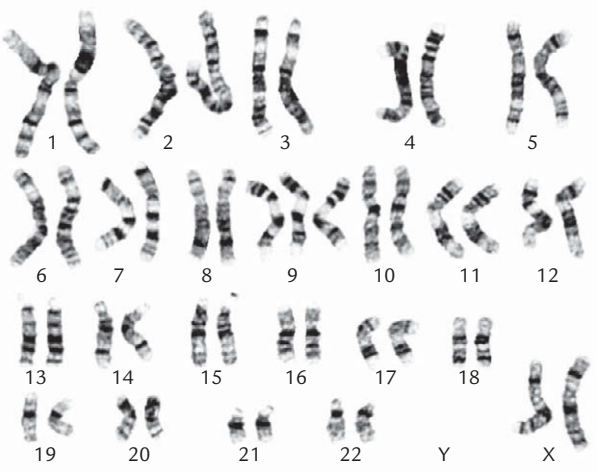

Figure 1. A karyotype of 47,XX,+9.

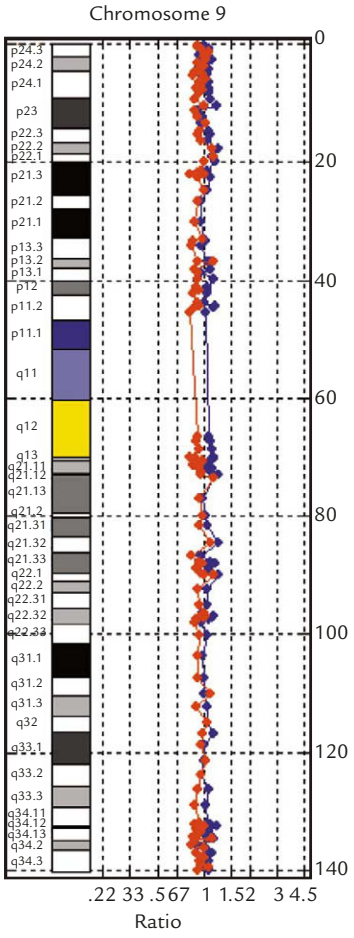

Figure 2. Array comparative genomic hybridization analysis of uncultured amniocytes shows no genomic imbalance in chromosome 9.

At 24 weeks of gestation, level II ultrasound showed bilateral ventriculomegaly. The parents elected to terminate the pregnancy. A 544 g malformed fetus was delivered with clenched hands, hypertelorism, a large

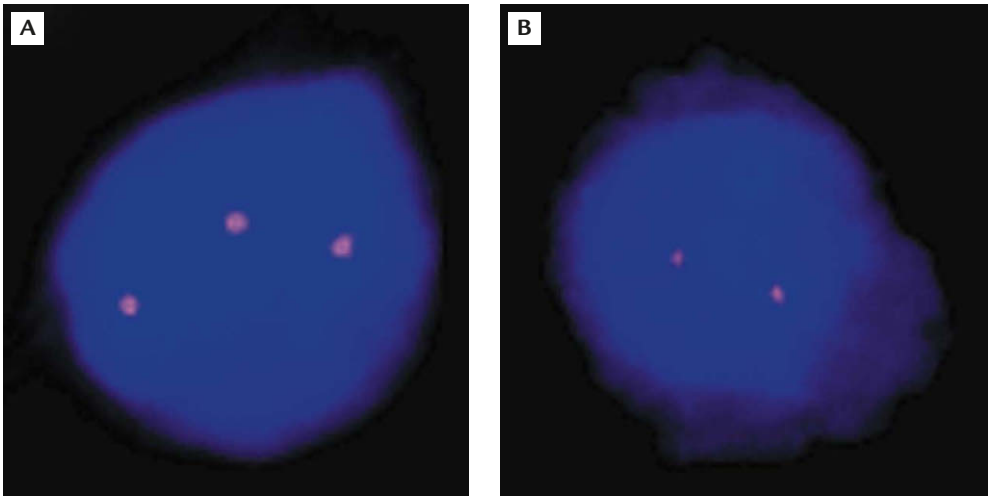

Figure 3. Fluorescence *in situ* hybridization analysis of uncultured interphase amniocytes shows (A) three signals in a cell with trisomy 9 and (B) two signals in a cell with disomy 9, consistent with the diagnosis of mosaic trisomy 9.

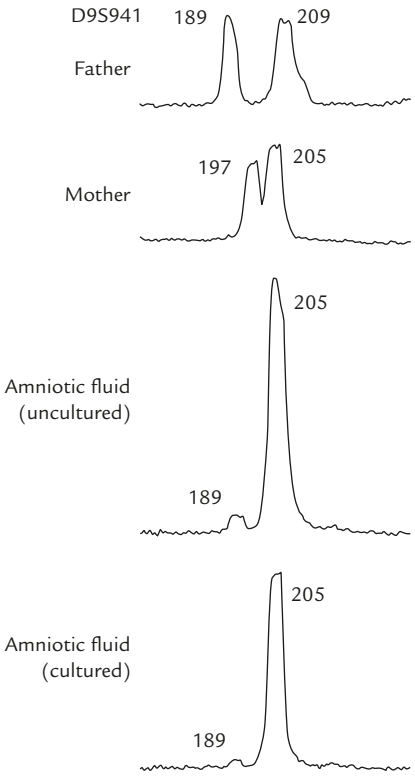

Figure 4. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays. The marker D9S941 shows two peaks (189 and 205 bp; paternal and maternal, respectively) of unequal fluorescent activity from two different parental alleles in uncultured amniocytes with a dosage ratio of 1:18 (paternal:maternal) and in cultured amniocytes with a dosage ratio of 1:36.

forehead, bilateral epicanthal folds, a broad nasal bridge, low-set posteriorly rotated ears, a thin upper lip, micrognathia, and a short neck (Figure 5).

Cytogenetic analyses of the fetal and extraembryonic tissues showed a karyotype of 47,XX,+9/46,XX.

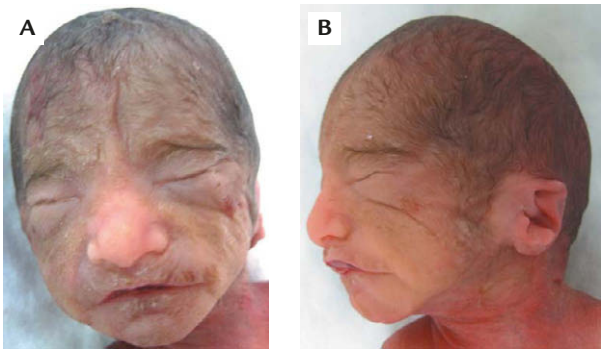

Figure 5. The proband at birth.

The levels of trisomy 9 in the cells of various tissues were 11% (11/100) in the cord blood, 5% (2/40) in the skin, 2.5% (1/40) in the lung, 22.5% (9/40) in the liver, 10% (4/40) in the cord, 17.5% (7/40) in the amnion, and 100% (40/40) in the placenta. Polymorphic DNA marker analyses of the uncultured fetal and extraembryonic tissues showed a diallelic pattern with unequal biparental inheritance of chromosome 9 (Figure 6). The uncultured tissues of cord, lungs, liver, skin, and cord blood had a paternal:maternal dosage ratio of 1:6, and the uncultured tissue of placenta had a dosage ratio of 1:2.

Discussion

The present case shows the usefulness of interphase FISH and QF-PCR, and the limitations of aCGH for the identification of low-level mosaicism for trisomy 9 at amniocentesis. The interphase FISH proved to be a very efficient method for confirmation of the status of mosaicism in the amniotic fluid sample prior to culture. The QF-PCR assay requires both parental samples and multiple polymorphic specific loci and shows

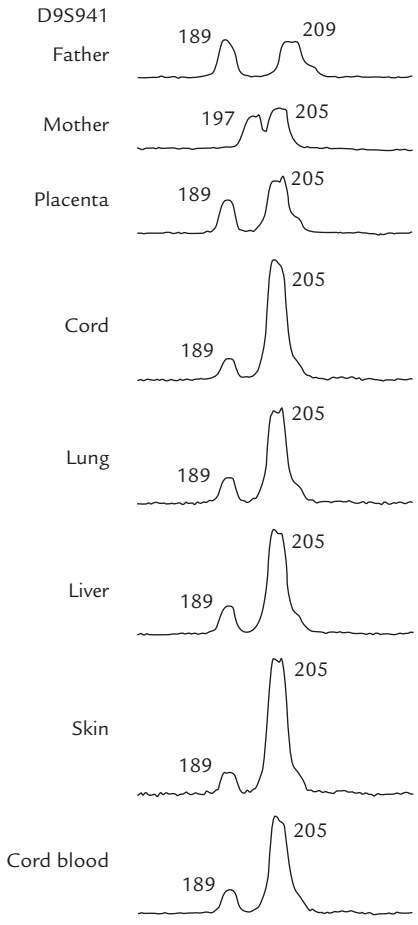

Figure 6. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays. The marker D9S941 shows two peaks (189 and 205 bp; paternal and maternal) of unequal fluorescent activity from two different parental alleles in the tissues of cord, lungs, liver, skin and cord blood with a dosage ratio of 1:6 (paternal:maternal) and in the placenta with a dosage ratio of 1:2.

limitations for the detection of a very low level of chromosomal mosaicism. Donaghue et al [15] suggested that the QF-PCR assay can detect mosaicism when the abnormal cell line comprises at least 15% of the whole sample. However, in this study, QF-PCR was able to detect the low-level mosaicism in uncultured and cultured amniocytes. aCGH can detect DNA dosage imbalances, including deletions and duplications, but shows limitations for the detection of low-level mosaicism, balanced translocations, inversions and polyploidy. Recent studies have suggested that aCGH can detect mosaicism as low as 20% in peripheral blood cells [16,17]. In this study, aCGH was unable to detect the low-level mosaicism of 18% (9/50) mosaic trisomy 9 in the uncultured amniocytes.

To date, at least 37 cases of prenatally detected mosaic trisomy 9 have been reported (Table). Of these 37 cases, 24 (64.9%) were associated with phenotypic abnormalities, suggesting a high risk of malformation in fetuses with prenatally detected mosaic trisomy 9. Among normal prenatal fetuses, the sex ratio is 1.07 (males/females). The Table shows that the sex ratio for fetal mosaic trisomy 9 is 0.21 (6/29), indicating a female preponderance in prenatally detected mosaic trisomy 9 and a prenatal selection against mosaic trisomy 9 males.

UPD can be observed together with a chromosomal aberration. Liehr [31] suggested that at least one-third of UPD cases are associated with or due to a chromosomal rearrangement. The phenotypic abnormalities of our case are more likely due to low-level mosaic trisomy 9 rather than the phenotypic effect of maternal UPD 9, because there is no evidence for an imprinting locus on maternal chromosome 9 [31–33]. UPD 9 can be associated with major clinical consequences only when a recessive mutation is reduced to homozygosity [34–36]. Sulisalo et al [34] reported UPD 9 with cartilage-hair hypoplasia because of a homozygous deletion of the *CHH* gene. Tiranti et al [35] reported UPD 9 with Leigh syndrome because of a homozygous loss of function mutation of the *SURF-1* gene. Castanet et al [36] reported maternal UPD 9 with syndromic congenital hypothyroidism because of homozygosity for a novel *FOXE1* mutation.

Cases with maternal UPD 9 have been reported to be associated with confined placental mosaicism for trisomy 9, low-level level II mosaic trisomy 9, low-level mosaic trisomy 9, and mosaic supernumerary ring chromosome 9 [r(9)] [12–14, 37]. Wilkinson et al [13] reported maternal UPD 9 in a fetus with mosaic trisomy 9 at chorionic villus sampling. Slater et al [14] reported maternal UPD 9 in a fetus with trisomy 9 at chorionic villus sampling, level II mosaic trisomy 9 (2.8%, 2 of 71 cells) at amniocentesis, low-level mosaic trisomy 9 (2.9%, 3 of 102 cells) at cordocentesis, and low-level mosaic trisomy 9 (8%, 4 of 50 cells) at neonatal blood sampling. The case was followed up to 1 year of age and had minor facial dysmorphism, skeletal abnormalities and growth retardation. Willatt et al [12] reported maternal UPD 9 in a 17-year-old man with growth and mental retardation, facial dysmorphism, skeletal abnormalities, and low-level mosaic trisomy 9 (7%, 7 of 100 cells) in the blood. Anderlid et al [37] reported maternal UPD 9 in a 10-month-old girl described by Blennow et al [38] with psychomotor retardation, moderate mental retardation, speech difficulties, no dysmorphic features, and a supernumerary r(9)(p10p12) in 36% of the lymphocytes. Björch et al [32] reported maternal isodisomy of UPD 9 in a 34-year-old woman with isochromosomes for the short and long arms of chromosome 9 without any clinical symptoms.

Table. Reported cases of prenatally detected mosaic trisomy 9

Author	Cases	Prenatal diagnosis	Confirmatory studies	Outcome and phenotype
Polani et al [18]	47,XX,+9/46,XX	Amniocentesis: T9 = NA	Fetal tissue: mosaic T9	TOP, abnormal abortus
Greenberg et al [19]	47,XX,+9/46,XX	Amniocentesis: T9 = 24% (58 cells)	Blood: 46,XX (75 cells) Amnion: 46,XX (75 cells)	Normal liveborn
Purvis-Smith et al [20]	47,XX,+9/46,XX	Amniocentesis: T9 = NA	NA	TOP, abnormal abortus facial dysmorphism, pulmonary stenosis, ASD, bicornuate uterus, dysmorphic hands and feet
Pfeiffer et al [21]	47,XX,+9/46,XX	Amniocentesis: T9 = 38% (47 cells)	Blood: 46,XX (50 cells) Skin: 46,XX (70 cells) Placenta: 47,XX,+9 (50 cells)	TOP, normal abortus
Zadeh et al [22]	47,XX,+9/46,XX	Amniocentesis: T9 = 84% (21/25 cells)	Skin: T9 = 26.3% (5/19 cells)	TOP, facial dysmorphism, ventriculomegaly, a single transverse kidney
Herens et al [23]	47,XX,+mar/ 47,XX,+9/46,XX	Amniocentesis: T9 = 38.7% (12/31 cells), SMC = 38.7% (12/31 cells) Fetal blood: T9 = 6% (3/50 cells), SMC = 68% (34/50 cells)	NA	TOP, minor external dysmorphism
Schwartz et al [24]	47,XX,+9/46,XX	Amniocentesis: T9 = 25% (13/52 cells) PUBS: T9 = 1% (1/100 cells) Repeat amniocentesis: T9 = 14% (14/100 cells)	Heart: T9 = 24% (50 cells) Skin: T9 = 13% (32 cells) Lung: T9 = 22% (50 cells) Liver: 46,XX (31 cells)	TOP, facial dysmorphism
Bureau et al [25]	47,XY,+9/46,XY	Ultrasound: DWM at 34 wk Amniocentesis: T9 = 50%	Blood: T9 = 30%	Delivery at 38 wk (2,510 g), facial dysmorphism, DWM, hydrocephalus, died at age 2 wk
Merino et al [26] Case 1	Mosaic T9	Ultrasound: IUGR, a globular stomach, microretrognathia Amniocentesis: T9 = 65%	NA	TOP, facial dysmorphism, a distended stomach with duodenal volvus

Table. (*Continued*)

Author	Cases	Prenatal diagnosis	Confirmatory studies	Outcome and phenotype
Case 2	47,XY,+9/46,XY	Ultrasound: IUGR Amniocentesis: T9 = 12% (12/100 cells) PUBS: 46,XY (100 cells)	Skin: T9 = 17% (17/100 cells) Lung: T9 = 14% (14/100 cells)	TOP, dolichocephaly, facial dysmorphism, bilateral hydronephrosis, glomerulocystic kidneys
Gross et al [27]	47,XX,+9/46,XX	Amniocentesis: T9 = NA	NA	TOP, abnormal abortus, unilateral choroid plexus cyst, two-vessel cord, micrognathia, renal dysplasia
Saura et al [28]				
Case 1	47,XX,+9/46,XX	CVS: 47,XX,+9 Amniocentesis: T9 = 64% (25 cells) PUBS: 46,XX (100 cells)	Skin: T9 = 16.1% (9/56 cells)	TOP, no external dysmorphic features
Case 3	47,XX,+9/46,XX	CVS: 47,XX,+9 Amniocentesis: T9 = 50% (25/50 cells) PUBS: T9 = 3% (3/100 cells)	NA	TOP, facial dysmorphism, PDA, horseshoe kidney
Case 4	47,XY,+9/46,XY	Ultrasound: PDA, polyhydramnios PUBS: T9 = 9% (9/100 cells)	Blood: 46,XY Skin: 46,XY	Delivery at 35 wk (1,500 g), facial dysmorphism, PDA
Case 6	47,XX,+9/46,XX	Ultrasound: IUGR PUBS: T9 = 2% (2/100 cells)	Blood: T9 = 6% (6/100 cells) Skin: 46,XX (100 cells)	Delivery at term (2,000 g), no dysmorphism except hip dislocation, developmental delay at age 21 mo
Hsu et al [8]				
Case IX-1	47,XX,+9/46,XX	Amniocentesis: T9 = 28% (25 cells)	Skin: T9 = 12.1% (7/58 cells)	TOP, normal abortus
Case IX-2	47,XX,+9/46,XX	Amniocentesis: T9 = 83.9% (31 colonies) PUBS: 46,XX (100 cells)	NA	Normal liveborn, normal at age 3 yr 8 mo
Case IX-3	Mosaic T9	Amniocentesis: NA	NA	TOP, abnormal abortus
Case IX-4	47,XX,+9/46,XX	Amniocentesis: T9 = 50% (48 cells)	Placenta: T9 = 80% (8/10 cells) Fetal tissue: T9 = 38.9% (7/18 cells)	TOP, abnormal abortus

Case IX-5	47,XX, +9/46,XX	Amniocentesis: T9 = 86.6% (30 cells)	Fetal tissue: 47,XX,+9 (5 cells)	TOP, abnormal abortus, facial dysmorphism, IUGR, ambiguous external genitalia
Case IX-8	47,XY,+9/46,XY	Amniocentesis: T9 = 30.4% (23 colonies)	Cord blood: T9 = 10% (3/30 cells) Placenta: 47,XXY,+ 9 (10 cells)	Normal fetus, died at age 4 d after premature birth
Case IX-9	47,XX,+9/46,XX	Amniocentesis: T9 = 8.3% (155 cells)	Skin: 46,XX (50 cells) Lung: 46,XX (50 cells)	TOP, normal abortus
Case IX-10	47,XX,+9/46,XX	Amniocentesis: T9 = 42% (40 cells)	NA	TOP, abnormal abortus, multiple congenital anomalies
Case IX-11	47,XX,+9/46,XX	Amniocentesis: T9 = 10% (39 cells)	Fetal tissue: 46,XX	TOP, normal abortus
Case IX-13	47,XX,+9/46,XX	Amniocentesis: T9 = 25% (32 colonies)	Skin and kidney: T9 = 40% (8/20 cells)	TOP, abnormal abortus, abnormal right big toe
Case IX-14	47,XY,+9/46,XY	Amniocentesis: T9 = 80% (15 colonies)	Kidney: T9 = 16% (4/25 cells) Villi: T9 = 28% Amnion: T9 = 33% Chorion: T9 = 34%	TOP, normal abortus
Case IX-15	47,XX,+9/46,XX	Amniocentesis: T9 = 15% (70 cells)	Blood: T9 = 16.7% (4/24 cells) Skin: 46,XX (20 cells)	Abnormal liveborn, IUGR, multiple congenital anomalies, facial dysmorphism
Case IX-16	47,XX,+9/46,XX	Amniocentesis: T9 = 12% (68 cells)	NA	TOP, abnormal abortus, facial dysmorphism, thick neck, bilateral tibia torsion
Case IX-21	47,XX,+9/46,XX	Amniocentesis: T9 = 58.6% (29 cells)	NA	TOP, abnormal abortus, ASD, pulmonary stenosis
Case IX-22	47,XX,+9/46,XX	Amniocentesis: T9 = 42% (40 cells)	NA	TOP, normal abortus
Case IX-23	47,XX,+9/46,XX	Amniocentesis: T9 = 7% (59 cells)	NA	TOP, normal abortus
Case IX-24	47,XY,+9/46,XY	Amniocentesis: T9 = 40% (59 cells)	Skin: 46,XY (50 cells)	TOP, normal abortus
Slater et al [14]	47,XX,+9/46,XX	CVS: 47,XX,+9 Amniocentesis: 47,XX,+9 (13 colonies), T9 = 2.8% (2/71 cells) (subculture) PUBS: T9 = 2.9% (3/102 cells)	Neonatal blood: T9 = 8% (4/50 cells)	Delivery at 38 wk (2,480 g), facial dysmorphism, growth retardation and skeletal abnormalities at age 1 yr

Table. (*Continued*)

Author	Cases	Prenatal diagnosis	Confirmatory studies	Outcome and phenotype
Tseng et al [29]	47,XX,+9/46,XX	Ultrasound: dolichocephaly, agenesis of left kidney, oligohydramnios, an intrahepatic cyst, varix of the portal vein Amniocentesis: T9 = 77.6% (38/49 cells)	Cord blood: T9 = 22.5% (9/40 cells)	TOP, facial dysmorphism, hydrocephalus, agenesis of left kidney, single umbilical artery, marked dilated portal vein
Chen et al [10]	47,XX,+9/46,XX	Amniocentesis: T9 = 75% (27/36 colonies)	Amnion: 46,XX (40 cells) Placenta: 46,XX (40 cells) Cord: T9 = 20% (8/40 cells) Liver: T9 = 35% (14/40 cells) Lung: T9 = 67.5% (27/40 cells) Skin: T9 = 5% (2/40 cells)	TOP, facial dysmorphism
Stipoljev et al [30]	47,XX,+9/46,XX	Ultrasound: bilateral hydronephrosis, short femur, oligohydramnios, placental cysts CVS: T9 = 31% PUBS: T9 = 6% (3/50 cells)	NA	TOP, facial dysmorphism, hydronephrosis, three kidneys, bicornuate uterus
Present case	47,XX,+9/46,XX	1st amniocentesis: T9 (1st) = 33.3% (3/9 colonies), 2nd amniocentesis: T9 = 24% (6/25 colonies), 3rd amniocentesis: T9 = 8.3% (2/24 colonies), Uncultured amniocytes: T9 = 18% (9/50 cells), interphase FISH	Cord blood: T9 = 11% (11/100 cells) Skin: T9 = 5% (2/40 cells) Lung: T9 = 2.5% (1/40 cells) Liver: T9 = 22.5% (9/40 cells) Cord: T9 = 10% (4/40 cells) Amnion: T9 = 17.5% (7/40 cells) Placenta: 47,XX,+9 (40 cells)	TOP, ventriculomegaly, facial dysmorphism

T9 = trisomy 9; TOP = termination of pregnancy; mar = marker; SMC = supernumerary marker chromosome; NA = not available; DWM = Dandy-Walker malformation; CVS = chorionic villus sampling; PUBS = percutaneous umbilical blood sampling; IUGR = intrauterine growth restriction; PDA = patent ductus arteriosus; ASD = atrial septal defect; FISH = fluorescence in situ hybridization.

In summary, there is a female preponderance in prenatally detected mosaic trisomy 9, and mosaic trisomy 9 can be associated with maternal UPD 9 in euploid cell lines. Mosaic trisomy 9 at amniocentesis carries a high risk of fetal abnormalities and should include detailed sonographic investigation of congenital malformations. aCGH shows limitations for the detection low-level mosaicism, whereas interphase FISH and QF-PCR are useful to confirm the status of mosaicism in the uncultured amniocytes.

Acknowledgments

This work was supported by research grants NSC-96-2314-B-195-008-MY3 and NSC-97-2314-B-195-006-MY3 from the National Science Council, and MMH-E-99004 from Mackay Memorial Hospital, Taipei, Taiwan.

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