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Short Communication

Mosaic trisomy 12 at amniocentesis: Prenatal diagnosis and molecular genetic analysis

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Abstract

Objective: This study is aimed at prenatal diagnosis of mosaic trisomy 12 and reviewing the literature.
Materials and Methods: A 34-year-old woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47,XX,+12[9]/46,XX[14]. She was referred to the hospital for genetic counseling. Repeated amniocentesis was performed at 22 weeks of gestation. Array comparative genomic hybridization (aCGH), interphase fluorescence *in situ* hybridization (FISH) and quantitative fluorescent polymerase chain reaction (QF-PCR) were applied on uncultured amniocytes, and conventional cytogenetic analysis was applied on cultured amniocytes.
Results: The aCGH analysis on uncultured amniocytes revealed a small genomic gain in chromosome 12. Interphase FISH analysis on uncultured amniocytes using a 12q11-q12-specific probe of RP11-496H24 (green spectrum) showed three green signals in 17.8% (8/45 cells) of uncultured amniocytes. QF-PCR analysis on uncultured amniocytes using chromosome 12-specific microsatellite markers excluded uniparental disomy 12. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47,XX,+12[5]/46,XX[25]. The parents decided to continue the pregnancy. A healthy 3270 g female baby was delivered at 39 weeks of gestation, with no phenotypic abnormalities. Cytogenetic analysis of the cord blood revealed a karyotype of 46,XX in 40/40 cultured lymphocytes. The neonate was normal in growth and psychomotor development at 6 months of age. Interphase FISH analysis on uncultured urinary cells revealed 5% (1/20 cells) mosaicism for trisomy 12.
Conclusion: Prenatal diagnosis of mosaic trisomy 12 at amniocentesis should alert a clinically significant aneuploidy. Interphase FISH and aCGH on uncultured amniocytes are useful for rapid confirmation of low-level trisomy 12 mosaicism at repeated amniocentesis.

Keywords: amniocentesis; mosaicism; mosaic trisomy 12; trisomy 12

Introduction

Mosaic trisomy 12 is one of the commonly described mosaicisms at amniocentesis that has been well described in the literature [1–20]. Postnatally diagnosed trisomy 12 mosaicism has a variable phenotype, and the reported phenotypic abnormalities include developmental delay, pigmentary dysplasia, congenital heart defects, microcephaly, facial asymmetry,

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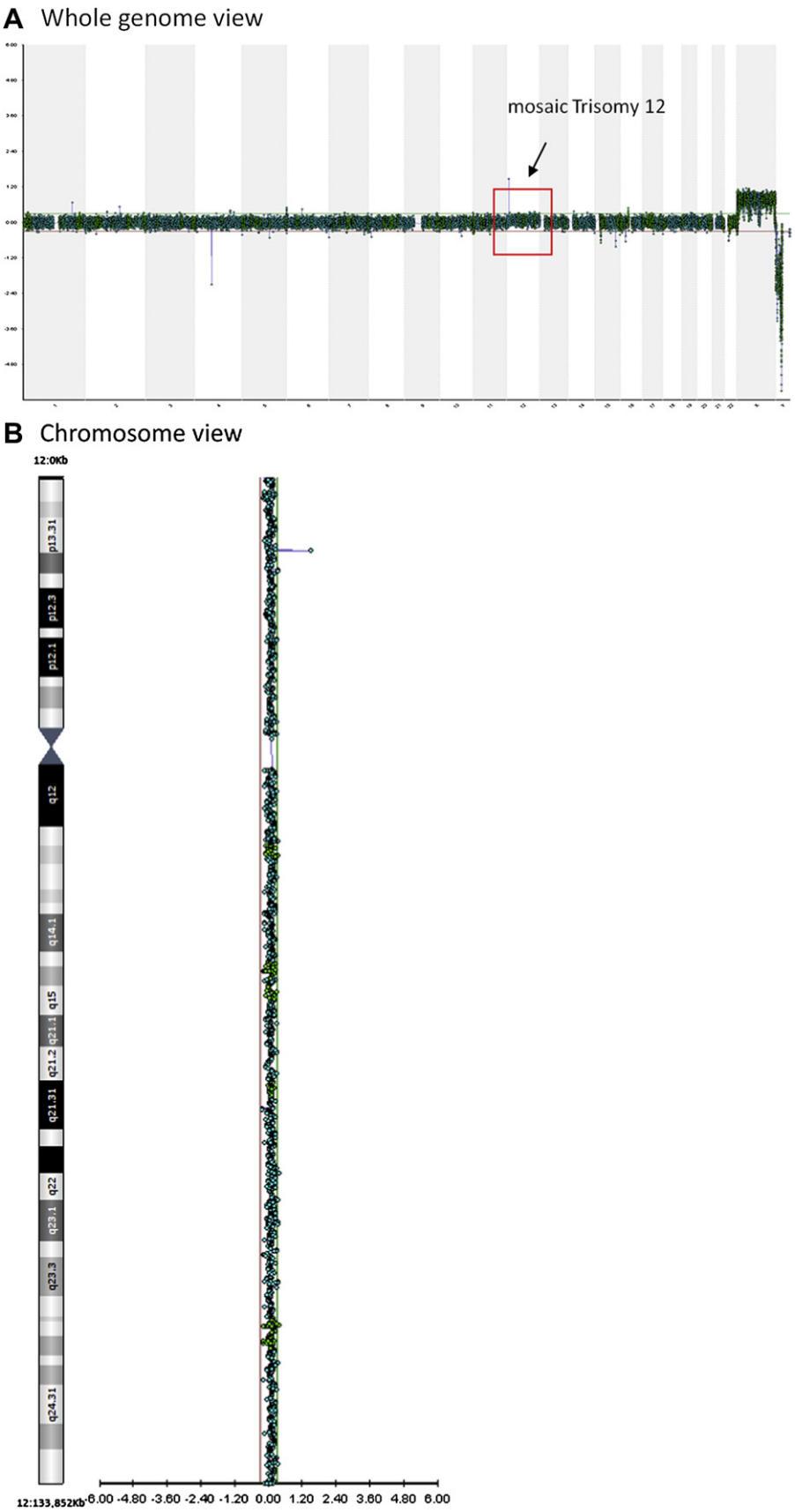

Fig. 1. Array comparative genomic hybridization analysis on uncultured amniocytes demonstrates a small genomic gain in chromosome 12. (A) Whole genome view; (B) chromosome view.

prominent ears, hypotonia, hemihyperplasia, intestinal malrotation, retinopathy, and sensorineural hearing loss [11,21–28]. Herein, we present our experience of prenatal diagnosis of mosaic trisomy 12 by amniocentesis and a review of the literature.

Materials and methods

A 34-year-old, gravida 3, para 1, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47,XX,+12[9]/46,XX[14]. She was referred to the hospital for genetic counseling. The parental karyotypes were normal, and prenatal ultrasound findings were unremarkable. Repeated amniocentesis was performed at 22 weeks of gestation. Array comparative genomic hybridization (aCGH), interphase fluorescence *in situ* hybridization (FISH) and quantitative fluorescent polymerase chain reaction (QF-PCR) were applied on uncultured amniocytes, and conventional cytogenetic analysis was applied on cultured amniocytes.

Results

The aCGH analysis using CytoChip Oligo Array (BlueGnome, Cambridge, UK) on uncultured amniocytes revealed a small genomic gain in chromosome 12 (Fig. 1). Interphase FISH analysis on uncultured amniocytes using a 12q11-q12-specific probe of RP11-496H24 (green spectrum) showed three green signals in 17.8% (8/45 cells) and two green signals in 82.2% (37/45 cells) of uncultured amniocytes (Fig. 2). QF-PCR analysis on uncultured amniocytes using chromosome 12-specific microsatellite markers revealed a 1:1 biparental diallelic pattern for chromosome 2 and thus excluded uniparental disomy (UPD) 12 (Fig. 3). Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47,XX,+12[5]/46,XX[25]. Of 30 colonies of cultured amniocytes, five colonies (16.7%) had the karyotype of 47,XX,+12 (Fig. 4), whereas the other 25 colonies (83.3%) had the karyotype of 46,XX. The parents decided to continue the pregnancy. A healthy 3270 g female baby was delivered at 39 weeks of gestation, with no phenotypic abnormalities. Cytogenetic analysis of cord blood revealed a karyotype of 46,XX in 40/40 cultured lymphocytes. The neonate was normal in growth and psychomotor development at 6 months of age. Interphase FISH analysis on uncultured urinary cells at the age of 6 months, using 12q11-q12-specific probe of RP11-496H24

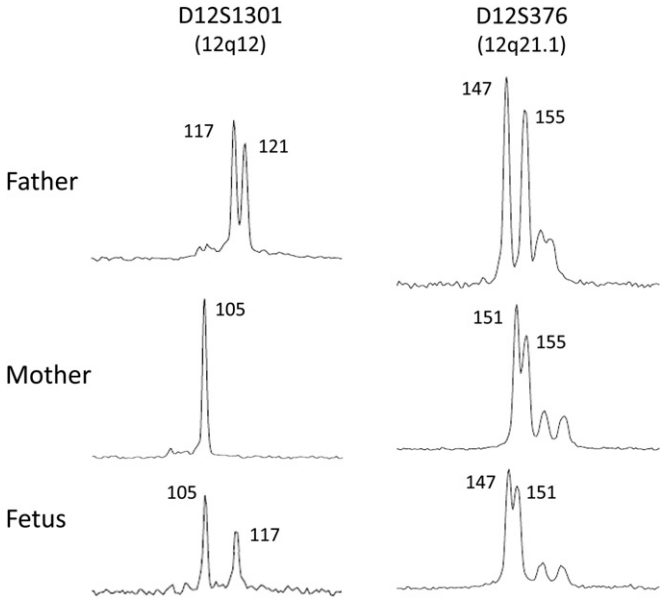

Fig. 3. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays on uncultured amniocytes. The markers D12S1301 and D12S376 show two peaks of equal fluorescent activity from two different parental alleles in uncultured amniocytes with a dosage ratio of 1:1 (paternal allele:maternal allele).

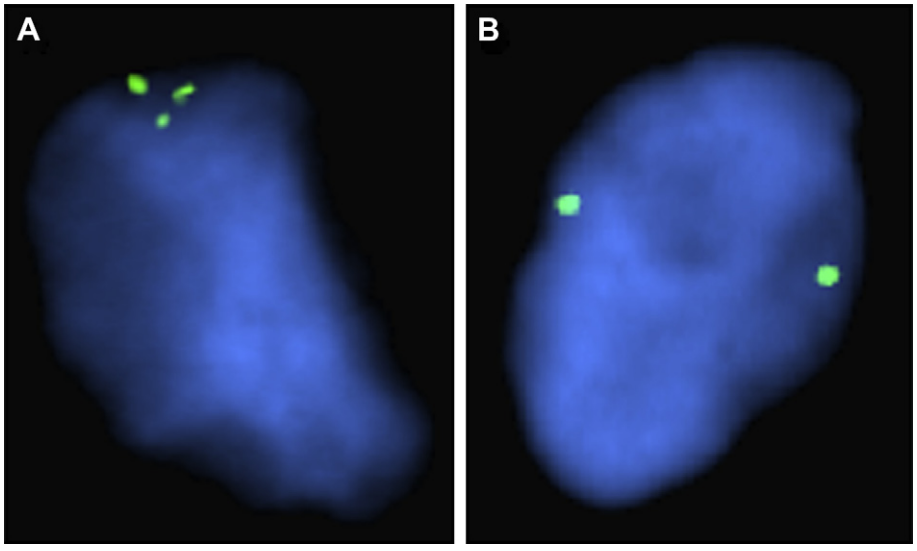

Fig. 2. Interphase fluorescence *in situ* hybridization analysis on uncultured amniocytes using the a 12q11-q12-specific probe RP11-496H24 (green spectrum) shows: (A) three green signals in a trisomy 12 cell; (B) two green signals in a disomy 12 cell.

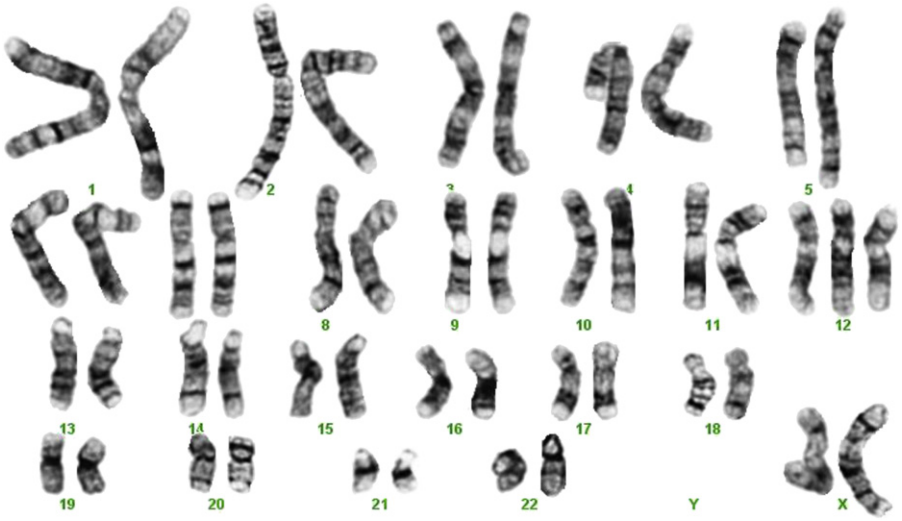

Fig. 4. A karyotype of 47,XX,+12.

(green spectrum), showed three green signals in 5% (1/20 cells) and two green signals in 95% (19/20 cells) of urinary cells, indicating 5% mosaicism for trisomy 12 in the urinary cells.

Discussion

Molecular cytogenetic techniques, such as aCGH, interphase FISH and QF-PCR, on uncultured amniocytes for rapid positive confirmation of trisomy mosaicism have been well described [29–34]. The present case shows that in case of trisomy 12 at amniocentesis, interphase FISH on uncultured amniocytes is useful for rapid confirmation of low-level mosaicism, aCGH on uncultured amniocytes is useful for confirmation of the presence of about 20% mosaicism, and QF-PCR assay on uncultured amniocytes is useful for rapid exclusion of UPD. The present case also provides evidence for a correlation of low-level trisomy 12 mosaicism in uncultured amniocytes with a favorable fetal outcome. In the present case, the first amniocentesis revealed 39.1% (9/23 colonies) mosaicism for trisomy 12 in cultured amniocytes, and the second amniocentesis revealed 16.7% (5/30 colonies) mosaicism for trisomy 12 in cultured amniocytes and 17.8% (8/45 colonies) mosaicism for trisomy 12 in uncultured amniocytes detected by interphase FISH. Different amniocenteses have been reported to result in inconsistent trisomy 12 mosaicism levels in cultured amniocytes and make genetic counseling difficult [7,9,13,20]. For examples, Frohlich and Falk [7] reported 7% versus 0%, Cartolano et al [9] reported 26.7% versus 0%, Spiro et al [13] reported 7.5% versus 48%, and Gentilin et al [20] reported 17.6% versus 62.5% mosaicism for trisomy 12 between two different amniocenteses. We think that interphase FISH on uncultured amniocytes in repeated amniocentesis is very practical for determining the real mosaicism level under such a circumstance.

To date, at least 32 cases of mosaic trisomy 12 detected by amniocentesis have been reported (Table 1). Of these, at least nine cases (9/32 = 28.1%) [3,4,11,14,16,17,19] were associated with prominent phenotypic abnormalities, suggesting that the malformation risk should be concerned in prenatal diagnosis of mosaic trisomy 12 by amniocentesis. In nine cases with an apparently abnormal outcome, the percentage of trisomic cells in cultured amniocytes varied from 4.3% to 61.9% (with 5 cases >34%). In 23 cases with a normal outcome, the percentage of trisomic cells in cultured amniocytes varied from 6.1% to 64.3% (with 3 cases > 34%). These findings indicate a correlation between a higher trisomy 12 mosaicism level and an abnormal fetal outcome. Table 1 shows that the male:female sex ratio for fetal mosaic trisomy 12 is 0.103 (3 males/29 females), indicating a female preponderance in fetal mosaic trisomy 12 and a natural selection against male mosaic trisomy 12 conceptuses. Table 1 also shows that mosaic trisomy 12 can prenatally be associated with elevated maternal serum α-fetoprotein [14], elevated maternal serum human chorionic gonadotrophin [12], abnormal maternal serum screening [12,14] and abnormal ultrasound findings [2,11,12]. Table 1 additionally shows that the reported abnormal ultrasound findings associated with mosaic trisomy 12 at amniocentesis include polyhydramnios, intrauterine growth restriction, single umbilical artery, congenital heart defects, hydronephrosis and absence of stomach image.

Mosaic trisomy 12 detected postnatally has been described in nine cases (2 males/7 females) [11,21–28]. Schinzel [35] concluded that there is no clinical pattern due to trisomy 12 mosaicism. Richer et al [21] first reported a 31-year-old phenotypically normal infertile man with 7% mosaicism for trisomy 12 in 157 peripheral blood lymphocytes and Kartagener syndrome of situs inversus, chorionic sinusitis, bronchitis and immotile spermatozoa. Patil et al [22] reported a 36-year-old moderately mentally retarded female with a karyotype of 47,XX,+12[7]/46,XX[49] in peripheral blood, facial dysmorphisms, short stature, microcephaly, muscle stiffness, areflexia limited extension of joints, waddling gaits and scoliosis. English et al [23] reported a 7-year-old mentally normal girl with a karyotype of 47,XX,+12[6]/46,XX[50] in skin fibroblasts, short stature, scoliosis, pigmentary dysplasia and

Table 1
Reported cases of mosaic trisomy 12 detected by amniocentesis.

Authors	Cases	Indication	Amniocentesis studies	Confirmatory studies	Outcome and phenotype
Jensen et al [1]	47,XX,+12/46,XX	Anxiety	Amniocentesis: T12 = 18% (68 cells)	Cord blood: T12 = 0% (215 cells) Skin: T12 = 0% (232 cells) Rib: T12 = 25% (12 cells)	TOP; normal abortus
Leschot et al [2]	47,XX,+12/46,XX	Polyhydramnios	Amniocentesis: T12 = 64.3% (14 colonies)	Cord blood: T12 = 0% (30 cells) Skin: T12 = 0% (30 cells) Urinary cells: culture A: T12 = 100% (12 cells) culture B: T12 = 23.3% (30 cells) Placenta: culture A: T12 = 31.3% (80 cells) culture B: T12 = 85% (60 cells)	Normal liveborn with hypoglycemia and convulsions after birth but normal development at age 9 mo
Watson et al [3]	Case 2 47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 61.9% (21 colonies)	Cord blood: T12 = 0%	Abnormal liveborn, 33 wk, 1710 g, CHD, cataracts, horseshoe kidneys, vertebral anomalies, neonatal death
Von Koskull et al [4]	47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 44% (16 cells)	Cord blood: T12 = 0% (100 cells) Blood: T12 = 0% (30 cells) Placenta: T12 = 100% (16 cells) Urinary cells: T12 = 0% (50 cells) Skin: T12 = 25% (20 cells)	Abnormal liveborn, CHD, facial dysmorphism, high arched palate, long thin fingers, proximally placed thumbs, neonatal death
Petrella and Hirschhorn [5]	47,XX,+12/46,XX	Anxiety	Amniocentesis: T12 = 11.1% (54 cells)	Skin: T12 = 0% (51 cells) Kidney: T12 = 0% (50 cells) Liver: T12 = 0% (18 cells) Placenta: T12 = 2.6% (39 cells)	TOP; normal abortus
Wyandt et al [6]	Case 1 47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 6.3% (32 colonies)	Subcutaneous tissue: T12 = 1.8% (109 cells) Bladder: T12 = 0% (70 cells) Membrane: T12 = 0% (34 cells) Placenta: T12 = 0% (35 cells) Peritoneum: T12 = 0% (63 cells) Blood: T12 = 0% (97 cells) Lung: T12 = 0% (60 cells)	TOP; normal abortus
	Case 2 47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 11.1% (63 cells)	Lung: T12 = 6% (50 cells)	TOP; normal abortus
	Case 3 47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 6.7% (60 cells)	NA	TOP; normal abortus
Frohlich and Falk [7]	47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 7% (86 cells) Retap: T12 = 0% (200 cells)	Blood: T12 = 0% (100 cells)	Normal liveborn, normal development at age 5 mo
Park et al [8]	47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 6.1% (98 cells)	Blood: T12 = 1% (98 cells) Skin: T12 = 3% (67 cells)	TOP; normal abortus
Cartolano et al [9]	47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 26.7% (15 colonies) Retap: T12 = 0% (7 colonies)	Cord blood: T12 = 0% (100 cells) Skin: T12 = 6.7% (15 cells) Placenta: T12 = 43% (72 cells)	TOP; normal abortus

(*continued on next page*)

Table 1 (*continued*)

Authors	Cases	Indication	Amniocentesis studies	Confirmatory studies	Outcome and phenotype
Meck et al [10]	47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 22.2% (36 colonies)	Cord blood: T12 = 0% (20 cells) Amnion: T12 = 0% (50 cells) Chorion: T12 = 0% (50 cells) Placenta: T12 = 0% (51 cells) Skin: T12 = 0% (100 cells)	Normal liveborn, normal development at age 5 y
Bischoff et al [11]	Case D 47,XX,+12/46,XX	AMA, ultrasound abnormalities	Amniocentesis: T12 = 4.3% (47 cells)	Cord blood: T12 = 0% (20 cells) Cord: T12 = 46.7% (30 cells) Placenta: T12 = 18.6% (32 cells) Membrane: T12 = 0% (30 cells)	Ultrasound: CHD, single umbilical artery, hydronephrosis. TOP; abnormal abortus, IUGR, single umbilical artery, hydronephrosis, facial dysmorphism, single palmar crease, truncus arteriosus
Brosens et al [12]	47,XX,+12/46,XX	AMA, elevated MSAFP, elevated MShCG, Down risk = 1/25, ultrasound abnormalities	Amniocentesis: T12 = 34.8% (69 cells)	Blood: T12 = 0% (30 cells) Skin: T12 = 0% (45 cells) Placenta: T12 = 87.5% (16 cells)	Ultrasound: no fetal stomach image at 22 wk, polyhydramnios at 32 wk, preterm birth Abnormal liveborn, 32 wk, 1990 g, aortic coarctation, right ventricular hypertrophy, tracheo-esophageal fistula, bilateral pleural effusions, pericardial effusion, neonatal death
Spiro et al [13]	47,XX,+12/45,X/46,XX	AMA	Amniocentesis: T12 = 7.5% (40 cells) Retap: T12 = 48% (50 cells)	Cord blood: T12 = 0% (50 cells) Placenta: T12 = 20% (20 cells) Villi: T12 = 32.5% (40 cells) Cord: T12 = 85% (20 cells) Membrane: T12 = 41.7% (60 cells) Skin: T12 = 15% (20 cells)	Normal liveborn, mild physical dysmorphisms, hypotonia, delay in gross motor development, age-appropriate cognitive development at age 18 mo
Hsu et al [14]	Case XI-1 47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 14.8% (27 colonies)	Fetal tissue: T12 = 7.5% (40 cells)	TOP; normal abortus, single umbilical artery
	Case XI-5 47,XY,+12/46,XY	Abnormal maternal serum triple screen	Amniocentesis: T12 = 6.3% (32 colonies)	NA	Normal liveborn
	Case XI-8 47,XY,+12/46,XY	NA	Amniocentesis: T12 = 33% (30 cells)	Fetal tissue: normal	TOP; normal abortus
	Case XI-9 47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 46.7% (15 colonies)	NA	TOP; normal abortus
	Case XI-10 47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 50% (24 colonies) Retaps: T12 = 53% T12 = 16%	NA	Epstein anomaly, finger overlapping, normal psychomotor development at age 8 mo

Table 1 (*continued*)

Authors	Cases	Indication	Amniocentesis studies	Confirmatory studies	Outcome and phenotype
	Case XI-11 47,XX,+12/46,XX	Elevated MSAFP	Amniocentesis: T12 = 12.5% (16 colonies) Retaps: T12 = 1.6% (61 colonies)	NA	Normal liveborn
	Case XI-12 47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 20% (20 colonies)	Cord blood: T12 = 0% (30 cells)	Normal liveborn
	Case XI-13 47,XY,+12/46,XY	Elevated MSAFP	Amniocentesis: T12 = 28.6% (14 colonies)	NA	Normal liveborn
	Case XI-14 47,XX,+12/46,XX	Elevated MSAFP	Amniocentesis: T12 = 23.3% (43 colonies)	Cord blood: T12 = 0% (50 cells)	TOP; abnormal abortus, facial dysmorphism, high arched palate, clinodactyly, transverse palmar creases, short colon, abnormal liver, CHD, large ovaries
	Case XI-18 47,XX,+12/46,XX	Elevated MSAFP	Amniocentesis: T12 = 32.1% (28 colonies)	NA	IUFD, IUGR, no gross abnormalities
Sikkema-Raddatz et al [15]	47,XX,+12/46,XX	AMA, mosaic trisomy 12 at CVS	Amniocentesis: T12 = 6.9% (29 colonies)	Cord: T12 = 0% T12 = 8% (100 cells) (FISH)	TOP; normal abortus
Djalali et al [16]	48,XX,+12,+13/46,XX	AMA	Amniocentesis: T12 and T13 = 17.7% (68 cells)	Skin: T12 = 1.3% (552 cells) (FISH) Rib: T12 = 2.8% (108 cells) (FISH)	TOP; abnormal abortus, facial dysmorphisms
Flore et al [17]	47,XX,+12/46,XX	AMA	Amniocentesis: mosaic T12	Blood: T12 = 0.6% (interphase cells) Placenta: T12 = 25% (cultured cells) Skin: T12 = 22% (cultured cells)	TOP; abnormal abortus, facial dysmorphisms, deep white matter microinfarct, subarachnoid congestion with focal hemorrhage, heterotopia of cerebellar white matter, broad and spaced hallices, prominent clitoris, poorly formed labia
Staals et al [18]	47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 18.2% (22 colonies)	NA	Normal liveborn, normal development at age 3 y
Daniel et al [19]	Case 6 47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 45.2% (42 colonies)	NA	TOP; abnormal abortus, facial dysmorphisms, abnormal nipples, unlobar right lung, dysplastic tricuspid valve, pleural effusion

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Table 1 (*continued*)

Authors	Cases	Indication	Amniocentesis studies	Confirmatory studies	Outcome and phenotype
Gentilin et al [20]	47,XX,+12/46,XX	Anxiety	Amniocentesis: T12 = 17.6% (17 colonies) Retap: T12 = 62.5% (40 colonies)	Skin: T12 = 2% (200 cells) Cartilage: T12 = 10% (200 cells)	TOP; normal abortus with mild micrognathia
Present case	47,XX,+12/46,XX	AMA	Amniocentesis: T12 = 39.1% (23 colonies) Retap: T12 = 16.7% (30 colonies) interphase FISH: T12 = 17.8% (45 uncultured amniocytes)	Cord blood: T12 = 0% (40 cells) Urinary cells: interphase FISH: T12 = 5% (20 cells)	Normal liveborn, normal development at age 6 mo

AMA = advanced maternal age; CHD = congenital heart defect; CVS = chorionic villus sampling; FISH = fluorescence *in situ* hybridization; IUFD = intrauterine fetal death; IUGR = intrauterine growth restriction; mo = month; MSAFP = maternal serum α-fetoprotein; MShCG = maternal serum human chorionic gonadotrophin; NA = not available; TOP = termination of pregnancy; T12 = trisomy 12; wk = week; y = year.

atrial septal defect. Bischoff et al [11] reported a male newborn with a karyotype of 46,XY in skin fibroblasts, a karyotype of 47,XY,+12[4]/ 46,XY[19] in chorionic villi, 5% (10/200) mosaicism for trisomy 12 in spleen, intrauterine growth restriction, oligohydramnios, Potter sequence, low-set ears, lung and kidney hypoplasia, and neonatal death. Aughton et al [24] reported a 9-year-old girl with a karyotype of 47,XX,+12[19]/48,XX,+12,+20[2]/46,XX[29] in skin fibroblasts, asymmetric fullness of the soft tissues of the face, trunk and extremities, normal growth and low-normal development. DeLozier-Blanchet et al [25] reported a 2-month-old girl with a karyotype of 47,XX,+12[7]/46,XX[38] in skin fibroblasts, congenital heart defects (large patent ductus arteriosus, dysplastic pulmonary and tricuspid valves), facial dysmorphisms, a two-vessel cord, widely spaced nipples, camptodactyly, overlapping fingers, pigmentary dysplasia and neonatal death. Boulard et al [26] reported a 15-year-old girl with 80% mosaicism for trisomy 12 in ovarian fibroblasts, pituitary stalk interruption, polycystic ovary syndrome, facial dysmorphisms, hypotonia, strabismus, conducting hearing loss and atrial septal defect. Parasuraman et al [27] reported a female newborn with a karyotype of 47,XX,+12[18]/46,XX[52] in cord blood, polyhydramnios, echogenic bowel and dilated cardiomyopathy on prenatal ultrasound, edema and low-set ears at birth, and neonatal death. Al-Hertani et al [28] reported a 25-month-old girl with a karyotype of 47,XX,+12[4]/46,XX[17] in the skin fibroblasts from hyperpigmented and hypopigmented regions, facial dysmorphisms, developmental delay, microcephaly, unilateral sensorineural hearing loss, intestinal malrotation, hemihyperplasia, pigmentary dysplasia, retinopathy and a vascular ring.

In summary, we present prenatal diagnosis and molecular cytogenetic analysis of mosaic trisomy 12 using uncultured and cultured amniocytes in a pregnancy with a favorable fetal outcome. We demonstrate the usefulness of analyses of uncultured amniocytes by interphase FISH and aCGH for rapid confirmation of low-level trisomy 12 mosaicism at amniocentesis, and by QF-PCR for rapid exclusion of UPD.

Acknowledgments

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