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Short Communication

Mosaic trisomy 15 at amniocentesis: Prenatal diagnosis, molecular genetic analysis and literature review

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ABSTRACT

Objective: To present prenatal diagnosis of mosaic trisomy 15 at amniocentesis.
Materials and methods: A 37-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,XY,+15[2]/46,XY[17]. She was referred for repeated amniocentesis at 19 weeks of gestation. Array comparative genomic hybridization (aCGH), interphase fluorescence *in situ* hybridization (FISH) and quantitative fluorescent polymerase chain reaction assays on uncultured amniocytes, conventional cytogenetic analysis and aCGH on cultured amniocytes, and FISH on uncultured urinary cells after birth were applied. Cordocentesis revealed a karyotype of 46,XY.
Results: At repeated amniocentesis, cultured amniocytes revealed a karyotypes of 46,XY [22 colonies], FISH on uncultured amniocytes revealed 21.2% (22/104 cells) mosaicism for trisomy 15, aCGH on uncultured amniocytes revealed a genomic gain (log2 ratio = 0.3) in chromosome 15, quantitative fluorescent polymerase chain reaction on uncultured amniocytes excluded uniparental disomy 15 (UPD 15), and aCGH on culture amniocytes revealed no genomic imbalance in chromosome 15. A healthy 3700 g male baby was delivered at 38 weeks of gestation with no phenotypic abnormalities at age 6 months. FISH on uncultured urinary cells at birth and at age 6 months revealed mosaic trisomy 15 levels of 20% (13/65 cells) and 12.2% (6/49 cells), respectively.
Conclusion: Prenatal diagnosis of mosaic trisomy 15 at amniocentesis should alert doctors about the occurrence of UPD 15 and a clinically significant phenotype. The present case provides evidence for cytogenetic discrepancy between uncultured and cultured amniocytes in mosaic trisomy 15 at amniocentesis. It is possible that the abnormal cell lines of amniocytes with trisomy 15 disappear after long-term cell culture.

Introduction

Mosaic trisomy 15 is a rarely described mosaicism at amniocentesis and in liveborn children. The common features of phenotypic abnormalities in liveborn children with mosaic trisomy 15 include intrauterine growth restriction (IUGR), congenital heart defects, multiorgan malformations and craniofacial dysmorphism [1–4]. In case of mosaic trisomy 15, there is an increased risk for

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maternal uniparental disomy for chromosome 15 [uniparental disomy 15 (UPD 15)], especially maternal uniparental heterodisomy for chromosome 15, and Prader–Willi syndrome because of trisomic rescue by reduction to disomy [1,5–9]. In this study, we present our experience of prenatal diagnosis of mosaic trisomy 15 by amniocentesis and a review of the literature.

Materials and methods

Clinical description

A 37-year-old, gravid 2, para 1 woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+15[2]/46,XY[17]. Among the 19 colonies of cultured amniocytes, two colonies had the karyotype of 47,XY,+15, whereas the other 17 colonies had a normal karyotype. 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 19 weeks of gestation. Array comparative genomic hybridization (aCGH), interphase fluorescence *in situ* hybridization (FISH), and quantitative fluorescent polymerase chain reaction (QF-PCR) assays were applied on uncultured amniocytes, and conventional cytogenetic analysis and aCGH were applied on cultured amniocytes. The woman underwent cord blood sampling at 23 weeks of gestation, which revealed a karyotype of 46,XY in 120 of 120 cells of cultured cord blood lymphocytes. The pregnancy was uneventful, and at 38 weeks of gestation, a healthy male baby was delivered with a body weight of 3700 g and a body length of 52.5 cm. The infant was doing well with no phenotypic abnormalities, and showed normal growth and psychomotor development at 6 months of age as checked by the pediatric specialist in medical genetics. Interphase FISH analysis on uncultured urinary cells was performed at birth and at the age of 6 months.

aCGH

Whole-genome aCGH on the DNA extracted from either uncultured amniocytes derived from 10 mL of amniotic fluid or cultured amniocytes was performed using NimbleGen ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA). The NimbleGen ISCA Plus Cytogenetic Array has 630,000 probes and a median resolution of 15–20 kb across the entire genome. The DNA from amniocytes was extracted first. This was done by following the manufacturer's protocol of QIAamp DNA Mini kit (Qiagen, Inc., Valencia, CA, USA). Then, the extracted DNA (0.5 μg) was labeled in Cy5 dye compared with an equivalent amount of normal female gDNA (G1521; Promega) labeled in Cy3 dye to perform the aCGH experiment. The experiment was performed according to the procedures recommended by the Roche NimbleGen ISCA plus Cytogenetic Array's user guide. The data were finally represented by using Nexus 6.1 (BioDiscovery, Hawthorne, CA, USA).

QF-PCR

QF-PCR analysis was performed on the DNA extracted from uncultured amniocytes and parental bloods. Briefly, primers specifically flanking short tandem repeat markers on chromosome 15 region such as D15S217 (15q13.1), D15S195 (15q22.2), D15S818 (15q24.1), D15S532 (15q26.1), and D15S816 (15q26.2) were applied to undertake polymorphic marker analysis to exclude UPD and to determine the parental origin of genomic imbalance if detected.

FISH

Interphase FISH analysis was performed on 104 uncultured amniocytes using a 15q11.2-specific bacterial artificial chromosome (BAC) probe RP11-441B20 encompassing 25,253,957–25,522,314 (NCBI build 37; spectrum green, fluorescein isothiocyanate) according to the standard FISH protocol. The same procedure was applied on 65 uncultured urinary cells obtained at birth. Interphase FISH analysis was applied on 49 uncultured urinary cells obtained at the age of 6 months using a 15q11.2-specific BAC probe RP11-307C10 encompassing 22,973,229–23,141,039 (NCBI build 37; spectrum red, Texas Red) and a 15q26.2-specific BAC probe RP11-79C10 encompassing 96,334,910–96,493,808 (NCBI build 37; spectrum green, fluorescein isothiocyanate).

Conventional cytogenetic analysis

Routine cytogenetic analysis by G-banding techniques at the 550 bands of resolution was performed following repeated amniocentesis. About 20 mL of amniotic fluid was collected, and the sample was subjected to *in situ* amniocyte culture. Twenty-two colonies of cultured amniocytes were investigated.

Results

Conventional cytogenetic analysis of cultured amniocytes at repeated amniocentesis revealed a karyotype of 46,XY in all of the 22 colonies of cultured amniocytes. At repeated amniocentesis, interphase FISH analysis on uncultured amniocytes showed three green signals of the 15q11.2-specific probe of RP11-441B20 in 21.2% (22/104) of the cells and two green signals in the remaining cells, indicating a 21.2% mosaicism for trisomy 15 in the uncultured amniocytes (Figure 1). The normal control database shows three signals in 0.9% (1/102) of the cells. Whole-genome aCGH analysis on the DNA extracted from uncultured amniocytes detected a gene dosage increase of chromosome 15 or arr 15q11.2q26.3 (20,110,602–102,531,392) × 2.46 (Figures 2 and 3). The duplicated segment had a log2 ratio of 0.3, indicating mosaicism in the uncultured amniocytes. However, aCGH analysis on the DNA extracted from the culture amniocytes revealed no genomic imbalance in chromosome 15, indicating no mosaicism in the cultured amniocytes (Figures 2 and 3). QF-PCR analysis on the DNA extracted from uncultured amniocytes and parental bloods revealed a biparental diallelic pattern for the chromosome 15-specific markers and thus excluded UPD 15 in the fetus (Figure 4). Interphase FISH analysis on uncultured urinary cells showed three green signals of RP11-

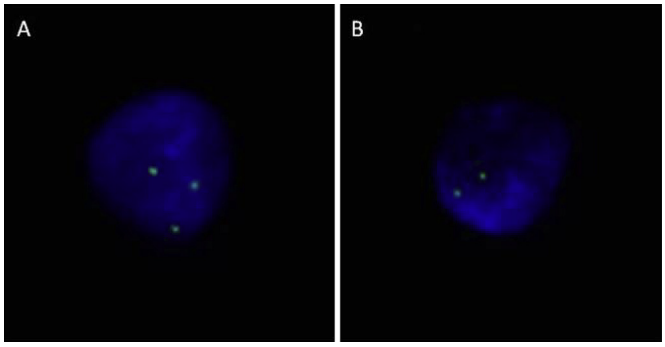

Figure 1. Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes using the 15q11.2-specific probe of RP11-441B20 [fluorescein isothiocyanate (FITC), spectrum green] shows (A) three green signals in a trisomy 15 cell and (B) two green signals in a disomy 15 cell.

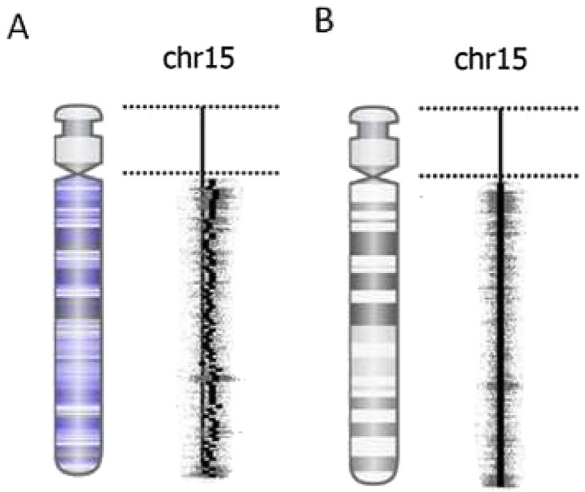

Figure 2. Array comparative genomic hybridization (aCGH) analysis reveals (A) a small genomic gain (a log2 ratio of 0.3) in chromosome 15 in uncultured amniocytes, and (B) no genomic imbalance in chromosome 15 in cultured amniocytes.

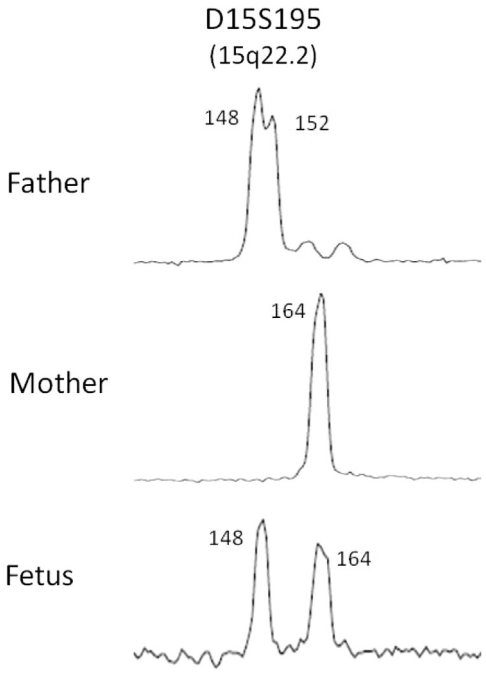

Figure 4. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays on the DNA extracted from uncultured amniocytes. The informative marker D15S195 (15q22.2) shows two peaks of fluorescent activity from two different parental alleles in uncultured amniocytes and thus excludes uniparental disomy 15.

441B20 in 20% (13/65) of the urinary cells obtained at birth, and three red signals of RP11-307C10 and three green signals of RP11-79C10 in 12.2% (6/49) of the urinary cells obtained at the age of 6 months (Figure 5).

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 [10–15]. The present case shows that in case of mosaic trisomy 15 at amniocentesis, interphase FISH and aCGH on uncultured amniocytes are useful for confirmation of the presence of mosaicism, and QF-PCR assay on uncultured amniocytes is useful for rapid exclusion of UPD 15. The present case also provides evidence

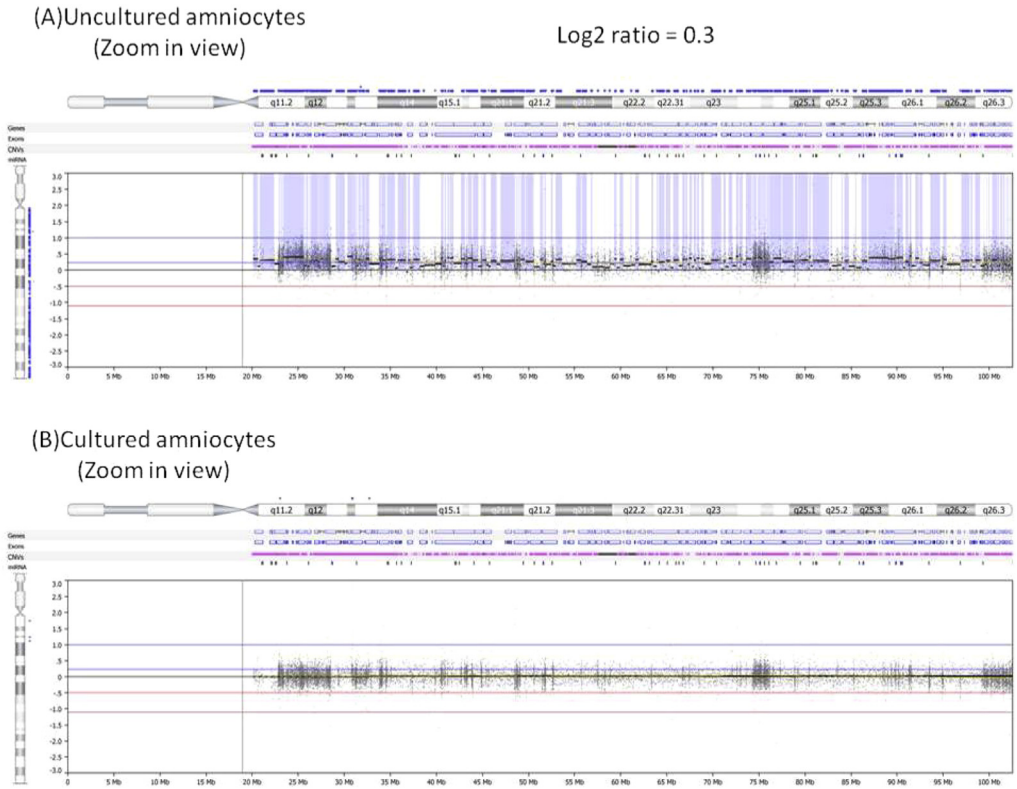

Figure 3. The zoom-in view of array comparative genomic hybridization (aCGH) on (A) uncultured amniocytes and (B) cultured amniocytes.

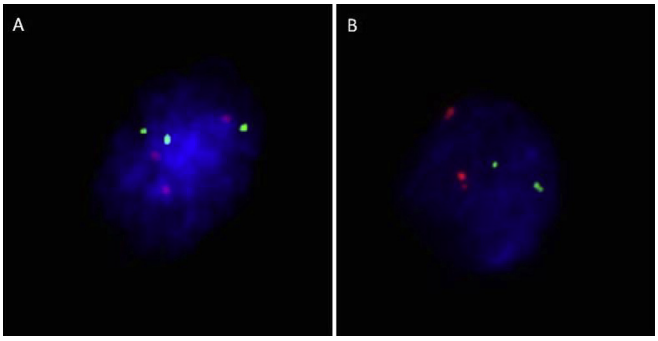

Figure 5. Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured urinary cells using the 15q11.2-specific probe of RP11-307C10 (Texas Red, spectrum red) and the 15q26.2-specific probe of RP11-79C10 [fluorescein isothiocyanate (FITC), spectrum green] shows (A) three green and three red signals in a trisomy 15 cell, and (B) two green and two red signals in a disomy 15 cell.

for a correlation of low-level mosaic trisomy 15 in uncultured amniocytes with a favorable fetal outcome. In the present case, the first amniocentesis revealed 10.5% (2/19 colonies) mosaicism for trisomy 15 in cultured amniocytes, but the second amniocentesis revealed no (0/22 colonies) mosaicism for trisomy 15 in cultured amniocytes, indicating that different amniocenteses may report in inconsistent mosaic trisomy 15 levels in cultured amniocytes, making genetic counseling even more difficult. The present case additionally provides evidence for cytogenetic discrepancy between uncultured amniocytes and cultured amniocytes in mosaic trisomy 15 at amniocentesis. At repeated amniocentesis in this case, uncultured amniocytes revealed ~ 21.2% mosaicism for trisomy 15 by interphase FISH, and < 30% mosaicism by aCGH, whereas in cultured amniocytes, no mosaic trisomy 15 was detected by conventional cytogenetic analysis and aCGH study. It is possible that the abnormal cell lines of amniocytes with trisomy 15 disappear after long-term cell culture. We suggest that application of

Table 1
Reported cases of mosaic trisomy 15 detected by amniocentesis.

Study	Cases	Indication	Amniocentesis	Confirmatory studies	Outcome & phenotype
Gimelli et al [32]	47,XX,+15/46,XX	AMA	T15 = 34.6% (26 cells) Retap: T15 = 28% (25 cells)	Skin: T15 = 56% (41 cells) Lung: T15 = 29.4% (17 cells) Left kidney: T15 = 14.8% (74 cells) Right kidney: T15 = 0% (23 cells) Intestine: T15 = 15% (20 cells)	Top; facial dysmorphism, CHD (persistent common AV canal), malrotation of intestine, abnormal rib numbers (13 ribs)
Worton & Stern [23]	Mosaic trisomy 15	—	T15 = 5.9% (51 cells)	Blood: T15 = 0% (50 cells)	Normal liveborn
Lahdetie & Lakkala [17]	47,XX,+15/46,XX	AMA	T15 = 9.9% (81 cells) Retap: T15 = 5.8% (34 cells)	Placenta: T15 = 92.4% (198 cells) Membrane: T15 = 47.1% (17 cells) Cord: T15 = 8.3% (121 cells) Cord blood: T15 = 0% (100 cells)	IUGR, oligohydramnios, delivered at 37 wk, 1420 g; CHD (hypoplastic left ventricle, mitral atresia, subvalvular aortic stenosis, ASD, VSD), died at age 13 d
Sundberg et al [18]	47,XX,+15/46,XX	AMA	T15 = 64% (78 colonies)	Cord blood: T15 = 5.6% (54 cells) Cord: T15 = 56% (25 cells) Skin: T15 = 72% (25 cells) Membrane: T15 = 0% (30 cells)	Prenatal ultrasound: mitral atresia, VSD, a hypoplastic left heart, TOP
Milunsky et al [16] Milunsky et al [5]	47,XX,+15/46,XX	Abnormal ultrasound, IUGR, low E3 = 0.38 MoM	T15 = 44.4% (9 colonies)	Blood: T15 = 0% (100 cells) Skin: T15 = 80% (50 cells) Lung: T15 = 85% (20 cells) Blood DNA: maternal UPD 15	IUGR, delivery at 38 wk; 1700 g, facial dysmorphism, CHD (VSD, PDA), hypotonia, abnormal ribs (13 ribs), overlapping fingers with hypoplastic nails; died at age 6 wk
Rocklin et al [6] Christian et al [7] Case 1	47,XX,+15/46,XX	AMA, previous child with Down syndrome	T15 = 44.4% (27 cells)	Skin: T15 = 100% (10 cells) Lung: T15 = 100% (10 cells) Kidney: T15 = 100% (10 cells) Membrane: T15 = 30% (10 cells) Cord blood: T15 = 18% (189 cells) DNA: maternal UPD 15	TOP; a two-vessel cord, malrotataion of the bowel
Christian et al [7] Case 2	47,XX,+15/46,XX	AMA	T15 = 66% (24 cells) Retap: T15 = 37% (30 cells)	CVS (direct): T15 = 33% (6 cells) (culture): T15 = 100% (6 cells) Cord blood: T15 = 17% (30 cells) Skin: T15 = 40% (20 cells) DNA: no UPD 15	IUGR, TOP; extension contraction of metacarpal −phalangeal joints on both upper extremities, low-set ears, arrhinencephaly
Case 3	47,XY,+15/46,XY	AMA	T15 = 6% (50 cells)	Retap: DNA: no UPD 15 PCR: no mosaicism	Delivery at 28 wk; normal
Markovic et al [19]	47,XX,+15/46,XX	AMA; T15 = 96.7% (30 cells) by CVS	T15 = 36% (50 cells) Retap: T15 = 29% (31 cells)	Heart blood: T15 = 23.5% (51 cells) Left kidney: T15 = 6% (50 cells) Right kidney: T15 = 9.2% (54 cells) Intestine: T15 = 44.4% (54 cells) Skin: T15 = 42.6% (54 cells) FISH: no UPD 15	TOP; craniofacial dysmorphism, brachycephaly
Zaslav et al [20] Zaslav et al [21]	47,XX,+15/46,XX	AMA	T15 = 5.1% (39 colonies)	Lung: T15 = 2% (50 cells) Heart: T15 = 8% (50 cells) Placenta: T15 = 100% (50 cells) Skin: T15 = 6% (50 cells) FISH Amniotic fluid: T15 = 19% (75 cells)	Abnormal ultrasound: IUGR, a hypoplastic right ventricle; TOP; single umbilical artery

(*continued on next page*)

Table 1 (*continued*)

Study	Cases	Indication	Amniocentesis	Confirmatory studies	Outcome & phenotype
				Lung: T15 = 5% (100 cells) Heart: T15 = 15% (100 cells) Placenta: T15 = 95% (100 cells) Skin: T15 = 10% (100 cells) DNA: no UPD 15	
Hsu et al [9]					
Case XIII-5	47,XY,+15/46,XY	—	T15 = 31.2% (48 cells)	—	Normal abortus
Case XIII-8	47,XX,+15/46,XX	AMA	T15 = 39.3% (28 cells)	Skin: T15 = 20% (10 cells) Cord: T15 = 50% (10 cells) Villi: T15 = 44.4% (9 cells) Membrane: T15 = 60% (10 cells) DNA: maternal UPD 15	TOP; abnormal abortus, IUGR
Case XIII-9	47,XX,+15/46,XX	Positive MSAFP profile	T15 = 6.1% (49 cells)	Blood: T15 = 0% (30 cells) Placenta: T15 = 0% (30 cells)	Normal liveborn
Case XIII-11	47,XY,+15/46,XY	—	T15 = 3.6% (83 cells) Retap: T15 = 1% (200 cells)	Cord blood: T15 = 0% (200 cells) Placenta: T15 = 72% (50 cells) Amnion: T15 = 86% (50 cells) Chorion: T15 = 91% (45 cells) Cord: T15 = 6% (50 cells)	Normal liveborn
Hansson et al [22]	45,X/47,XY,+15/46,XY	Anxiety	T15 = 10.5% (19 colonies) 45,X = 10.5% (19 colonies) Retap: T15 = 3.8% (26 colonies) 45,X = 50% (26 colonies)	Cord blood: T15 = 0% (30 cells) 45,X = 0% (30 cells) Lung: T15 = 20% (30 cells) 45,X = 20% (30 cells) Kidney: T15 = 0% (25 cells) 45,X = 44% (25 cells) Fasia: T15 = 12% (25 cells) 45,X = 28% (7 cells) Placenta: T15 = 36% (25 cells) 45,X = 44% (25 cells) DNA: no UPD 15	TOP; normal abortus
Present case	47,XY,+15/46,XY	AMA	T15 = 10.5% (19 colonies) Retap: T15 = 0% (22 colonies) FISH (uncultured amniocytes): T15 = 21.2% (104 cells) aCGH (uncultured amniocytes): T15 log2 ratio = 0.3 aCGH (cultured amniocytes): no genomic imbalance QF-PCR: (uncultured amniocytes): no UPD 15	Cord blood: T15 = 0% (120 cells) FISH (uncultured urinary cells): At birth: T15 = 20% (65 cells) At age 6 mo: T15 = 12.2% (49 cells)	Delivery at 38 wk; 3700 g. Normal at birth & at age 6 mo

— = not available; aCGH = array comparative genomic hybridization; AMA = advanced maternal age; ASD = atrial septal defect; AV = atrioventricular, CHD = congenital heart defect; CVS = chorionic villus sampling; E3 = estriol; FISH = fluorescence *in situ* hybridization; IUGR = intrauterine growth restriction; MoM = multiples of the median; MSAFP = maternal serum α-fetoprotein; PCR = polymerase chain reaction; PDA = patent ductus arteriosus; QF-PCR = quantitative fluorescent polymerase chain reaction; T15 = trisomy 15; TOP = termination of pregnancy; UPD = uniparental disomy; VSD = ventricular septal defect.

interphase FISH and aCGH on uncultured amniocytes at repeated amniocentesis for mosaic trisomy 15 is very practical for determining the real mosaic level under such a circumference.

To date, at least 16 cases (including this case) of mosaic trisomy 15 detected by amniocentesis have been reported (Table 1). Of these, at least 9 cases (9/15 = 56.3%) [5–7,9,16–22,32] were associated with prominent phenotypic abnormalities, suggesting that the malformation risk should be given consideration in prenatal diagnosis of mosaic trisomy 15 by amniocentesis. In the 9 cases with an apparently abnormal outcome, the percentage of trisomic cells in cultured amniocytes varied from 5.1% to 66% (with 7 cases ≥ 28%). In the seven cases with a normal outcome, the percentage of trisomic cells in cultured amniocytes varied from 1% to 31.2% (with 4 cases ≤ 6.1%). These findings indicate a correlation between a higher trisomy 15 mosaicism level and an abnormal fetal outcome. Table 1 shows that the male/female sex ratio for fetal mosaic trisomy 15 is 0.5 (5 males/10 females), indicating a female preponderance in fetal mosaic trisomy 15. Table 1 also shows that mosaic trisomy 15 can prenatally be associated with elevated maternal serum α-fetoprotein [9], decreased maternal serum estriol [5,16], and abnormal ultrasound findings [5,7,9,16–18,20,21]. The reported abnormal ultrasound findings associated with mosaic trisomy 15 at amniocentesis include IUGR, oligohydramnios, and congenital heart defects. In the present case, the cord blood sampling revealed a normal karyotype. Table 1 shows a limitation of application of cord blood sampling for the confirmation of mosaic trisomy 15 detected by amniocentesis [5,9,16,17,22,23]. At least three cases in Table 1 were associated with maternal UPD 15 [5–7,9,16]. Therefore, in case of mosaic trisomy 15 detected by amniocentesis, the UPD testing to detect maternal uniparental disomy, particularly heterodisomy for chromosome 15, should be considered—especially when cord blood sampling or repeated amniocentesis reveals a normal karyotype. Maternal UPD 15 and paternal UPD 15 are syndromic [24,25]. Maternal UPD 15 is associated with Prader–Willi syndrome, which is characterized by muscular hypotonia, feeding difficulties, hyperphagia, obesity, moderate mental retardation, facial dysmorphisms, short hands and feet, and hypogonadotropic hypogonadism [24,25]. Paternal UPD 15 is associated with Angelman syndrome, which is characterized by seizures, electroencephalographic abnormalities, ataxia,

severe mental retardation, jerky movements, and inappropriate laughter [24,25].

To date, at least 12 cases (4 males/8 females) of liveborn cases with mosaic trisomy 15 have been reported [1–5,16,17,26–31]. The observed abnormalities associated with mosaic trisomy 15 included IUGR, craniofacial dysmorphisms; renal anomalies of small dysplastic kidneys and bilateral pelviectasis; brain anomalies of hypoplastic cerebellum, ventricular asymmetry, lenticulostriate vasculopathy, and defects of anterior interhemispheric falx; genital anomalies of anteriorly placed anus, hypoplastic labia majora, undescended testis, hypoplastic scrotum, and small penis; congenital heart defects of ventricular septal defect, coarctation of aorta, hypoplastic left ventricle, mitral atresia, subvalvular aortic stenosis, atrial septal defect, patent ductus arteriosus, mitral stenosis, and pulmonary stenosis; digit anomalies, and pigmentary abnormalities [4]. The present case has 20% mosaicism for trisomy 15 in the uncultured amniocytes and the urinary cells at birth, but presented no phenotypic abnormalities at the age of 6 months at follow-up.

In summary, we present prenatal diagnosis and molecular cytogenetic analysis of mosaic trisomy 15 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 15 mosaicism at amniocentesis, and by QF-PCR for rapid exclusion of UPD 15.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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