Mosaic Trisomy 7 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 7.

Materials, Methods and Results: A 38-year-old primigravid woman underwent amniocentesis at 19 weeks of gestation because of her advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+7[26]/46,XY[16]. Repeated amniocentesis at 21 weeks of gestation revealed a karyotype of 47,XY,+7[20]/46,XY[17]. Simultaneous cordocentesis revealed a karyotype of 46,XY in 100/100 cultured lymphocytes. Polymorphic DNA marker analyses of uncultured amniocytes and cord blood revealed a diallelic pattern with seemingly equal biparental inheritance of chromosome 7. Repeated cordocentesis and chorionic villus sampling at 23 weeks of gestation revealed a karyotype of 47,XY,+7[2]/46,XY[66] in cord blood and a karyotype of 47,XY,+7 in 24/24 cultured chorionic villi cells. Level II ultrasonography was normal. At 40 weeks of gestation, a 2,708 g normal male baby was delivered. The peripheral blood had a karyotype of 46,XY in 100/100 lymphocytes. Molecular analyses of placenta, urine, buccal swab, and peripheral blood revealed a diallelic pattern and seemingly equal biparental inheritance of chromosome 7 in all tissues. At 3 months of age, he manifested hypopigmented skin and inguinal hernia, but showed normal growth and mental development. Fluorescence *in situ* hybridization analysis of inguinal hernia sac tissue revealed that 19/100 (19%) of nuclei had three chromosome 7 signals.

Conclusion: Mosaic trisomy 7 at amniocentesis may be derived from a cell culture artifact from an undetected low level of trisomy 7 mosaicism in uncultured amniocytes, and can be associated with favorable fetal outcome if the blood has a normal karyotype or a very low level of mosaicism and if uniparental disomy for chromosome 7 is excluded. [*Taiwan J Obstet Gynecol* 2010;49(3):333–340]

Key Words: amniocentesis, mosaicism, mosaic trisomy 7, trisomy 7, uniparental disomy for chromosome 7

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 7 mosaicism has variable and nonspecific clinical features [4–8]. Most patients with trisomy 7 mosaicism have a normal karyotype in blood lymphocytes, but mosaic trisomy 7 in fibroblasts derived from the skin show pigment abnormalities. Trisomy 7 mosaicism at amniocentesis has been reported to be associated with maternal uniparental disomy for chromosome 7 (UPD 7) and Silver-Russell syndrome (SRS) [9–11]. Here, we report the prenatal diagnosis and molecular

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genetic analyses of mosaic trisomy 7 at amniocentesis in a pregnancy with a favorable fetal outcome.

Materials, Methods and Results

A 38-year-old primigravid woman underwent amniocentesis at Mackay Memorial Hospital at 19 weeks of gestation because of her advanced maternal age. The woman had suffered from bilateral tubal occlusion and primary infertility. This was her first pregnancy that was conceived by *in vitro* fertilization and embryo transfer. Four embryos had been implanted and three survived. The triplet pregnancy had three gestational sacs. At 7 weeks of gestation, fetal demise occurred in two fetuses. The remaining singleton fetus developed well at the time of amniocentesis.

In 26 of 42 separated amniocyte colonies, an abnormal karyotype of 47,XY,+7 was found (Figure 1), while the other 16 colonies had a karyotype of 46,XY. The cytogenetic result of amniocentesis was 47,XY,+7 [26]/46,XY[16]. The parental karyotypes were normal. Repeated amniocentesis at 21 weeks of gestation revealed 47,XY,+7[20]/46,XY[17]. Simultaneous cord blood sampling revealed a karyotype of 46,XY in 100/100 cultured lymphocytes. Polymorphic DNA marker analysis of the cord blood and uncultured amniocytes using microsatellite markers specific for chromosome 7 revealed a biparental inheritance of chromosome 7. There was a diallelic pattern and seemingly equal biparental inheritance of chromosome 7 in the cord blood and uncultured amniocytes (Figure 2). The molecular result excluded UPD 7.

At 23 weeks of gestation, the woman underwent repeated cord blood sampling and chorionic villus sampling at National Taiwan University Hospital. Cytogenetic analyses showed that the cord blood lymphocytes had a karyotype of 47,XY,+7[2]/46,XY[66], and the chorionic villi had a karyotype of 47,XY,+7 in 24/24 cultured chorionic villi cells. A methylation-specific polymerase chain reaction (PCR) assay was performed to identify the differential methylation of the imprinted *PEG1/MEST* locus on 7q32 and revealed biparental inheritance of chromosome 7 in the cord blood and chorionic villi (Figure 3). Polymorphic DNA

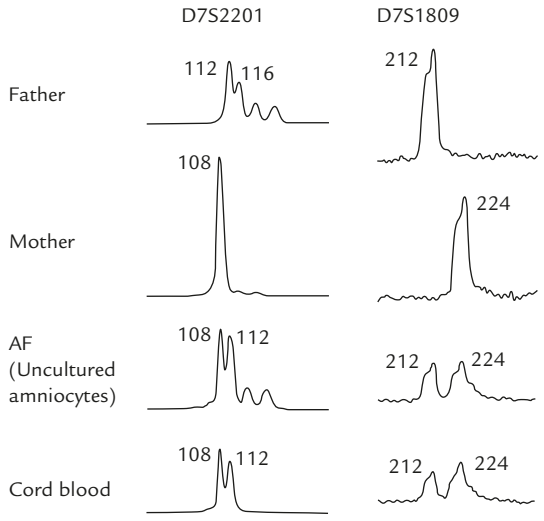

Figure 2. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays at short tandem-repeat markers specific for chromosome 7. The marker D7S2201 shows two peaks (108 and 112 bp; maternal and paternal) of seemingly equal fluorescent activity from two different parental alleles in uncultured amniocytes from the amniotic fluid sample and cord blood. The marker D7S1809 also shows two peaks (212 and 224 bp; paternal and maternal, respectively) of seemingly equal fluorescent activity from two different parental alleles. AF = amniotic fluid.

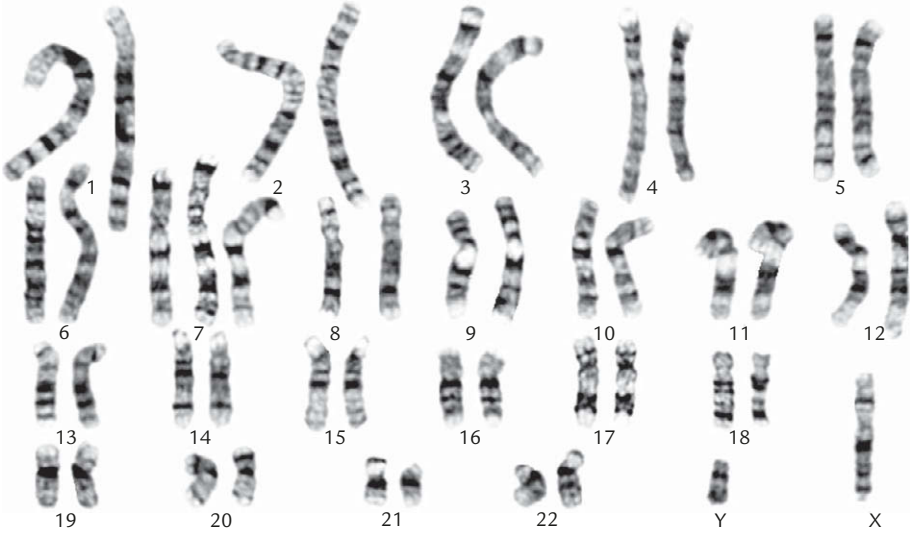

Figure 1. Karyotype of 47,XY,+7.

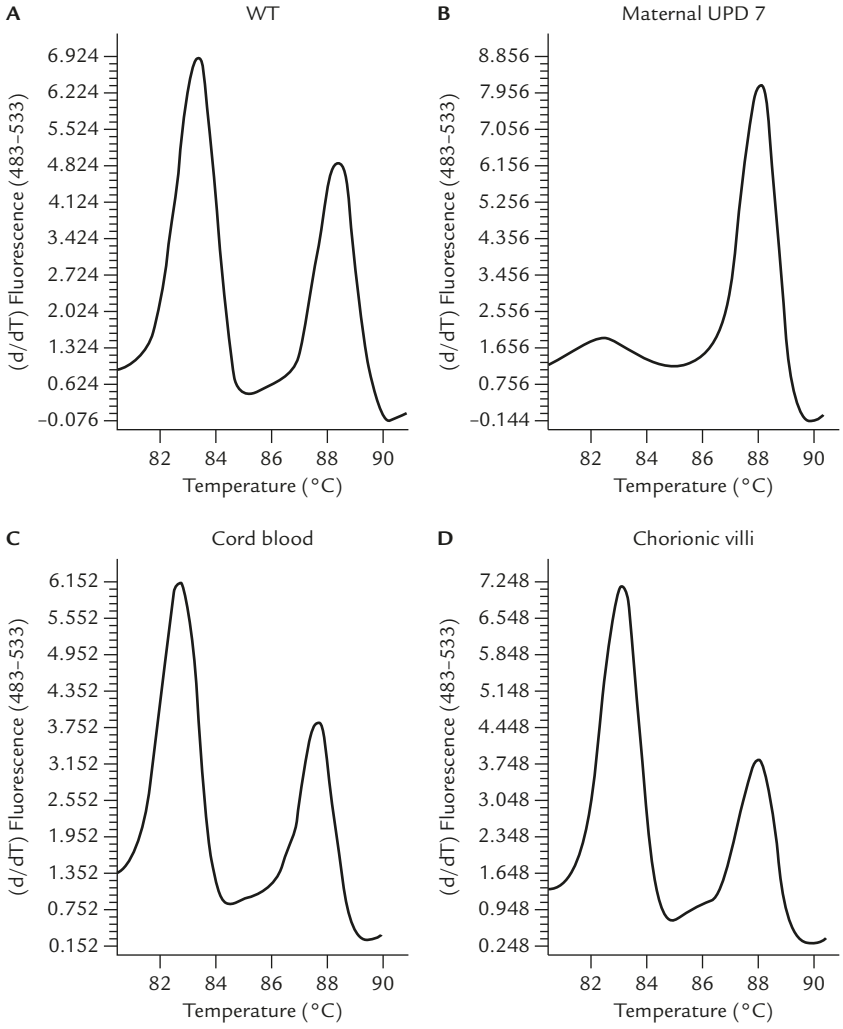

Figure 3. Polymerase chain reaction (PCR) products from bisulfite-modified DNA, using an unmethylated allele-specific primer pair and a methylated allele-specific primer pair on the methylation-sensitive high resolution melting PCR assay. (A) a normal subject with the wild-type methylated and unmethylated alleles; (B) a subject with maternal uniparental disomy of chromosome 7 with only the methylated allele; (C) cord blood; (D) chorionic villi.

marker analysis of the chorionic villi cells revealed a diallelic pattern with unequal biparental inheritance of chromosome 7 with a dosage ratio of 1:2 (paternal allele:maternal allele) (Figure 4).

Level II obstetric ultrasonography revealed normal fetal growth biometry, a normal fetal craniofacial profile, and no structural abnormalities. The parents decided to continue the pregnancy. At 40 weeks of gestation, a 2,708 g male baby was delivered uneventfully at Mackay Memorial Hospital. The baby was normal without pigment abnormalities of the skin. Cytogenetic analysis of the peripheral blood lymphocytes (100 cells) of the neonate revealed a karyotype of 46,XY. Polymorphic DNA marker analyses of placenta, urine, buccal swab, and peripheral blood cells of the neonate revealed a diallelic pattern with seemingly equal biparental inheritance of chromosome 7 in all tissues examined (Figure 5).

At a routine pediatric follow-up examination at 3 months of age, the infant showed normal growth and mental development. He manifested hypopigmented skin on both thighs and underwent herniorrhaphy for inguinal hernia. Fluorescence *in situ* hybridization (FISH) analysis in the pathological specimen of the inguinal hernia sac tissue revealed that 19/100 (19%) of nuclei had three chromosome 7 signals indicating mosaic trisomy 7 in the inguinal hernia sac tissue.

Discussion

The present case provides evidence for a discrepancy between the cytogenetic results of cultured amniocytes and the molecular results of uncultured amniocytes in mosaic trisomy 7 at amniocentesis. The high level of

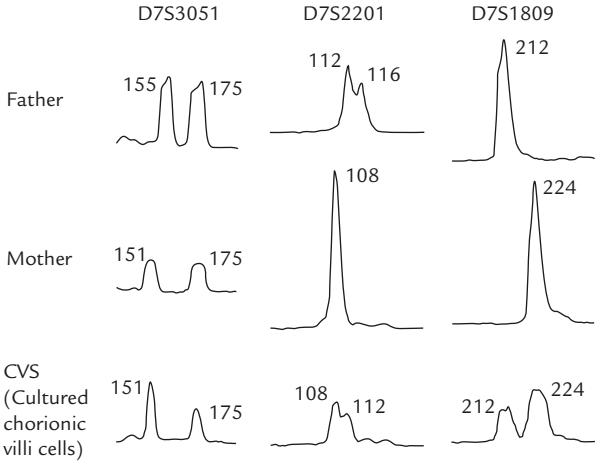

Figure 4. Representative electrophoretograms of quantitative fluorescent polymerase chain raction assays at short tandem-repeat markers specific for chromosome 7. The marker D7S1809 shows two peaks (212 and 224 bp; paternal and maternal) of unequal fluorescent activity from two different parental alleles. The dosage ratio was 1:2 in cultured chorionic villi cells. The markers D7S3051 and D7S2201 also show a diallelic pattern with a dosage ratio of 1:2 (paternal:maternal). The results are consistent with trisomy 7 of maternal origin. CVS = chorionic villus sampling.

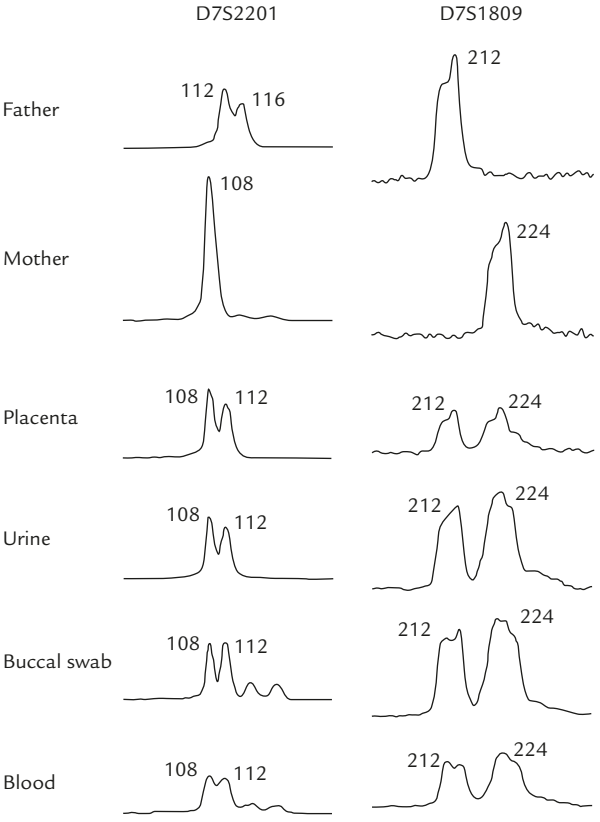

Figure 5. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays at short tandem-repeat markers specific for chromosome 7. The marker D7S2201 shows two peaks (108 and 112 bp; maternal and paternal) of seemingly equal fluorescent activity from two different parental alleles in placenta, urine, buccal swab, and peripheral blood cells. The marker D7S1809 also shows a diallelic pattern with seemingly equal fluorescent activity from two different parental alleles.

trisomy 7 in cultured amniocytes might be derived from a cell culture artifact from an undetected low level of trisomy 7 mosaicism in the uncultured amniocytes. In the present case, although various tissues presented a diallelic pattern with seemingly equal biparental inheritance of chromosome 7, a very low level of trisomy 7 mosaicism cannot be completely excluded.

The quantitative fluorescent polymerase chain reaction (QF-PCR) assay shows limitations for the detection of very low levels of chromosomal mosaicism. The QF-PCR assay can detect mosaicism when the abnormal cell line contributes at least 15% of the whole sample [12]. In a cohort study performed to detect mosaicism of primary trisomies in prenatal samples by QF-PCR and karyotype analysis, Donaghue et al [12] found that the QF-PCR assay detected mosaicism when a meiotically derived abnormal cell line contributed 15% of the genotype, but mitotically derived mosaicism might not be detected at this low level.

At least 13 cases of mosaic trisomy 7 detected at amniocentesis have been reported (Table). The reported fractions of trisomy 7 cells or colonies range from 5% to 78%. Among those cases, nine had a normal phenotype and four had phenotypic abnormalities, of which two were associated with maternal UPD 7 and SRS [9–11]. Maternal UPD 7 is the mostly frequently reported UPD, second to UPD 15. Maternal UPD 7 is characterized by pre- and postnatal growth retardation, relative macrocephaly, micrognathia, a high arched palate, down-turned corners of the mouth, a triangular facial shape, and neuropsychological developmental delay [16,17]. Paternal UPD 7 is rare, and only three cases have been reported to date [18–20]. Paternal UPD 7 has been reported in several autosomal recessive disorders such as chloride diarrhea, cystic fibrosis, complete situs inversus, and immotile cilia. Paternal UPD 7 can be associated with developmental delay and overgrowth [20]. Maternal complete isodisomy 7 should be the result of a post-zygotic mitotic segregation error, whereas maternal heterodisomy 7 should be the result of trisomic rescue after a meiotic non-disjunction event at the first meiotic cell division [21,22].

SRS (OMIM 180860) is characterized by severe intrauterine growth restriction (IUGR), poor postnatal growth, craniofacial features of a triangular-shaped face with a broad forehead, down-turned corners of the

Table. Reported cases of mosaic trisomy 7 at amniocentesis

Author	Karyotype	Proportion of abnormal AF cells or colonies (total)	Confirmatory studies	Phenotype
Jenkins et al [7]	47,XY,+7/46,XY	23% (39 cells)	46,XY (60 cells): blood 47,XY,+7 (26 cells)/46,XY (10 cells): skin	Developmental delay, facial asymmetry, epilepsy, hypomelanosis of Ito, bifid uvula, enamel dysplasia at 7 yr
Hsu et al [13]				
Benn, case VII-1	47,XY,+7/46,XY	48% (25 colonies)	46,XY (100 cells): blood 47,XY,+7 (11 cells)/46,XY (11 cells): foreskin	Normal at 4½ yr
Bradshaw & Jones, case VII-2	47,XY,+7/46,XY	36.6% (30 cells) 18.2% (33 cells) (retap)	46,XY (203 cells): cord blood 46,XY (100 cells): blood 47,XY,+7 (18 cells)/46,XY (20 cells): foreskin	Normal at 4 yr
Fadness, case VII-3	47,XX,+7/46,XX	5% (141 cells)	46,XX: blood 46,XX: placenta	Normal at birth
Neu, case VII-5	47,XX,+7/46,XX	31.3% (16 colonies)	46,XX (30 colonies): amniotic fluid 46,XX (30 cells): cord 46,XX (20 cells): villi	Normal at birth
Neu, case VII-6	47,XX,+7/46,XX	26.7% (15 colonies)	No	Normal at birth
Shaffer, case VII-7	47,XY,+7/46,XY	15% (20 cells)	46,XY (30 cells): cord blood	Normal at 25 mo
Van Dyke, case VII-8	47,XY,+7/46,XY	11.4% (44 cells)	No	Normal at 4 mo
Kivirikko et al [14]	47,XY,+7/46,XY	78% (9 colonies)	46,XY (100 cells): cord blood 46,XY (100 cells): blood 47,XY,+7 (36 cells)/46,XY (64 cells): pigmented skin 47,XY,+7 (24 cells)/46,XY (76 cells): hypopigmented skin	Mentally normal, hypopigmented skin, facial asymmetry, sparse hair, short left palpebral fissure, ptosis of the left eyelid, strabismus, enamel dysplasia, posterior-rotated low-set ears, undescended testes at 4 yr
Bilimoria & Rothenberg [9]; Font-Montgomery et al [10]	47,XX,+7/46,XX	41% (32 colonies)	47,XX,+7 (19 cells): chorionic villi 46,XX (50 cells): cord blood Maternal UPD 7: cord blood 47,XX,+7 (9 cells)/46,XX (20 cells): skin Maternal UPD 7: skin	Small for gestational age, posterior-rotated low-set ears, prominent forehead, small chin, triangular face, obstructed left nares, prominent nasal bridge, reversed epicanthal folds, thin lip, small mouth, micrognathia, clinodactyly of the fifth fingers bilaterally, a bridged simian crease on the left hand, a two-vessel cord at birth Silver-Russell syndrome with short stature growth deficiency, persistent hypoglycemia, psychomotor developmental delay during infancy

Table. (*Continued*)

Author	Karyotype	Proportion of abnormal AF cells or colonies (total)	Confirmatory studies	Phenotype
Chen et al [15]	47,XX,+7/46,XX	16.7% (18 colonies) 12% (25 colonies) (retap)	46,XX (40 cells): chorionic villi 46,XX (35 cells): cord blood, No UPD 7 46,XX (40 cells): amniotic membrane, No UPD 7 46,XX (40 cells): placenta, No UPD 7 46,XX (40 cells): cord, No UPD 7 46,XX (40 cells): liver, No UPD 7 46,XX (40 cells): lungs, No UPD 7 46,XX (40 cells): skin, No UPD 7	Normal at 22 wk of gestation
Flori et al [11]	47,XY,+7/46,XY	44% (26 colonies)	47,XY,+7 (27 cells)/46,XY (17 cells): placenta 46,XY (100 cells): blood Maternal UPD 7: blood 46,XY (100 cells): cord 47,XY,+7 (15 cells)/46,XY (85 cells): intestine 47,XY,+7 (100 cells): skin FISH analysis: trisomy 7 30/220 nuclei (13.6%): healthy colon 29/210 nuclei (13.8%): colon with hypoganglionosis 8/145 metaphases (5.5%): skin 13/300 nuclei (4.3%): skin	Prominent large forehead, prominent nasal bridge, low posterior-rotated ears, small and retruded chin, bilateral clinodactyly of fifth fingers and bilateral simian creases at birth Silver-Russell syndrome with growth retardation, hypotonia, a small triangular-shaped face, learning disability. Hirschsprung's disease, short stature during infancy
Present case	47,XY,+7/46,XY	61.9% (42 colonies) 54.1% (37 colonies) (retap)	46,XY (100 cells): cord blood, No UPD 7 47,XY,+7 (2 cells)/46,XY (66 cells): cord blood (retap), biparental inheritance of chromosome 7 (methylation-specific PCR) 46,XY (100 cells): peripheral blood, No UPD 7, seemingly equal biparental inheritance (QF-PCR) Placenta: No UPD 7, seemingly equal biparental inheritance (QF-PCR) Buccal swab: No UPD 7, seemingly equal biparental inheritance (QF-PCR) Urine: No UPD 7, seemingly equal biparental inheritance (QF-PCR) FISH analysis: trisomy 7, 19/100 nuclei (19%): inguinal hernia sac	Normal at term. Mentally normal, hypopigmented skin on thighs and inguinal hernia at 3 mo

UPD = uniparental disomy; AF = amniotic fluid; FISH = fluorescence in situ hybridization; QF-PCR = quantitative fluorescent polymerase chain reaction.

mouth, a small mandible, prominent ears, fifth finger clinodactyly, asymmetry of the face, body and limbs, occasional genital anomalies, and café-au-lait spots [23]. Imprinting defects on 11p such as epimutations in 11p15 imprinting center region 1 represents 30% of the cases with SRS, and maternal UPD 7 represents about 5% of the cases with SRS [24,25]. Prenatal diagnosis of mosaic trisomy 7 should raise suspicion of UPD 7, although UPD 7 associated with prenatally diagnosed mosaicism is thought to be rare [26].

Prenatal diagnosis of UPD 7 can be achieved by QF-PCR by genotyping the fetus and the parents with microsatellite markers to identify the loss of one parental contribution, or with methylation-specific PCR [27–29]. Polymorphic DNA marker analysis requires samples from both parents and multiple polymorphic specific loci, whereas the methylation-specific PCR assay can specifically distinguish maternal and paternal alleles, and identify the differential methylation of the imprinted *PEG1/MEST* locus without requiring parental samples. The human *PEG1/MEST* gene is an imprinted gene on chromosome 7q32. *PEG1/MEST* is expressed from the paternal allele but not from the maternal allele [30]. Kaneko-Ishino et al [31] designated it as *PEG1* (paternally expressed gene 1) because of its paternal expression, and Sado et al [32] referred to it as *MEST* (mesoderm-specific transcript) because of its predominant expression in the mesoderm and its derivatives.

The assessment of DNA methylation at specific sites can be performed by bisulfite treatment of DNA or by digestion with methylation-sensitive restriction enzymes. In CpG methylation, a methyl group can be attached to a cytosine base located at 5′ to guanosine. After bisulfite treatment, sodium bisulfite converts unmethylated cytosine to uracil, whereas methylated cytosine in the CpG dinucleotide is resistant to this chemical modification.

Flori et al [11] suggested that SRS patients with maternal UPD 7 might also result from an undetected low level of trisomy 7 mosaicism. SRS is well known to present with IUGR, short stature and limb asymmetry on prenatal ultrasound [33–35]. Accordingly, prenatal diagnosis of mosaic trisomy 7 at amniocentesis should include detailed sonographic investigation of IUGR, short stature and asymmetry, and a molecular genetic analysis of UPD 7 in the cord blood.

In conclusion, mosaic trisomy 7 at amniocentesis may be derived from a cell culture artifact from an undetected low level of trisomy 7 mosaicism in the uncultured amniocytes, and can be associated with favorable fetal outcomes if the blood has a normal karyotype or a very low level of mosaicism and if UPD 7 is excluded.

Acknowledgments

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