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Case Report

Prenatal diagnosis of mosaic tetrasomy 18p

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Abstract

Objective: To present prenatal diagnosis and molecular cytogenetic characterization of a small supernumerary marker chromosome derived from isochromosome 18p, by interphase fluorescence *in situ* hybridization (FISH) on uncultured amniocytes.
Case Report: A 41-year-old woman underwent amniocentesis at 18 weeks of gestation, because of advanced maternal age. Amniocentesis revealed a *de novo* supernumerary isochromosome 18p in two of 14 colonies of cultured amniocytes. Repeated amniocentesis was performed at 22 weeks of gestation. Interphase FISH analysis on uncultured amniocytes showed four 18p11.32-specific probe (RP11-324G2) signals in 5.7% (3/53 cells) of uncultured amniocytes. A multiplex ligation-dependent probe amplification P095 test kit and array comparative genomic hybridization analysis did not detect genomic imbalance in chromosome 18. Cytogenetic analysis of cultured amniocytes at repeated amniocentesis revealed a karyotype of 47,XY,+i(18)(p10)[3]/46,XY[23]. The pregnancy was carried to 38 weeks of gestation, and a healthy 3120 g male baby was delivered. When examined at 2 months of age, the infant was normal in growth and development, without phenotypic abnormalities. The cord blood had a karyotype of 46,XY. Polymorphic DNA marker analysis excluded uniparental disomy 18. Interphase FISH analysis on uncultured urinary cells showed 9.4% (3/32 cells) mosaicism for tetrasomy 18p.
Conclusion: There is cytogenetic discrepancy between amniocytes and cord blood lymphocytes in prenatally detected mosaic tetrasomy 18p. Interphase FISH on uncultured amniocytes has the advantage of rapid confirmation of low-level mosaicism for tetrasomy 18p at amniocentesis.

Keywords: isochromosome 18p syndrome; mosaic tetrasomy 18p; prenatal diagnosis; supernumerary isochromosome 18p

Introduction

Tetrasomy 18p, or supernumerary isochromosome 18p, is a rare chromosome aberration that occurs in approximately 1 in 180,000 live individuals in the general population of Europe and affects both genders equally [1]. The majority of reported cases with tetrasomy 18p appear to be *de novo* events, although familial cases have been reported [2–4]. Isochromosome 18p syndrome (OMIM 614290) includes common abnormal findings of cognitive impairment, microcephaly, abnormal brain magnetic resonance imaging findings, growth retardation, feeding problems, developmental delay,

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strabismus, abnormal muscle tone, scoliosis, kyphosis, neonatal jaundice, respiratory distress, recurrent otitis media, hearing loss, seizures, refractive errors, constipation, gastroesophageal reflux, cryptorchidism, congenital heart defects and foot anomalies, and minor findings of hernia, kidney defects, myelomeningocele and short stature [5–6]. It has been suggested that in the majority of the cases, tetrasomy 18p, or supernumerary isochromosome 18p, results from maternal meiosis II nondisjunction immediately, followed by meiotic or early postmeiotic mitotic misdivision at the centromere, suggesting the maternal age may play a role in the formation of the supernumerary isochromosome 18p [7–9]. The phenotype of mosaic tetrasomy 18p, however, has variation ranging from an apparently normal phenotype, to multiple abnormalities [10–15]. Here, we present our experience of prenatal diagnosis of low-level mosaic tetrasomy 18p with a favorable outcome.

Case report

A 41-year-old, gravida 2, para 1, woman was referred for genetic counseling at 21 weeks of gestation, because of prenatally detected mosaic isochromosome 18p by amniocentesis. Her husband was 41 years old, and there was no family history of congenital malformations. She underwent amniocentesis at 18 weeks of gestation, because of advanced maternal age. In two out of 14 separated colonies of cultured amniocytes, an abnormal karyotype of 47,XY,+i(18)(p10) was noted, while the other 12 colonies had a karyotype of 46,XY. The karyotype was 47,XY,+i(18)(p10)[2]/46,XY[12] (Fig. 1). The parental karyotypes were normal. Level II ultrasound findings were unremarkable. She underwent repeated amniocentesis at 22 weeks of gestation. Interphase fluorescence *in situ* hybridization (FISH) on uncultured amniocytes, using an 18p11.32-specific probe (RP11-324G2) (spectrum red), showed four red signals in 5.7% (3/53 cells) of uncultured amniocytes and two red signals in 94.3% (50/53 cells) of uncultured amniocytes (Fig. 2). A multiplex ligation-dependent probe amplification P095 test kit and array comparative genomic hybridization analysis did not detect genomic imbalance in chromosome 18. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47,XY,+i(18)(p10)[3]/46,XY[23]. Prenatal ultrasound findings were normal. The parents decided to continue the pregnancy. A healthy 3120 g male baby was delivered at 38 weeks of gestation. Postnatal analysis of cord blood revealed a karyotype of 46,XY (20 cells). Polymorphic DNA marker analysis on cord

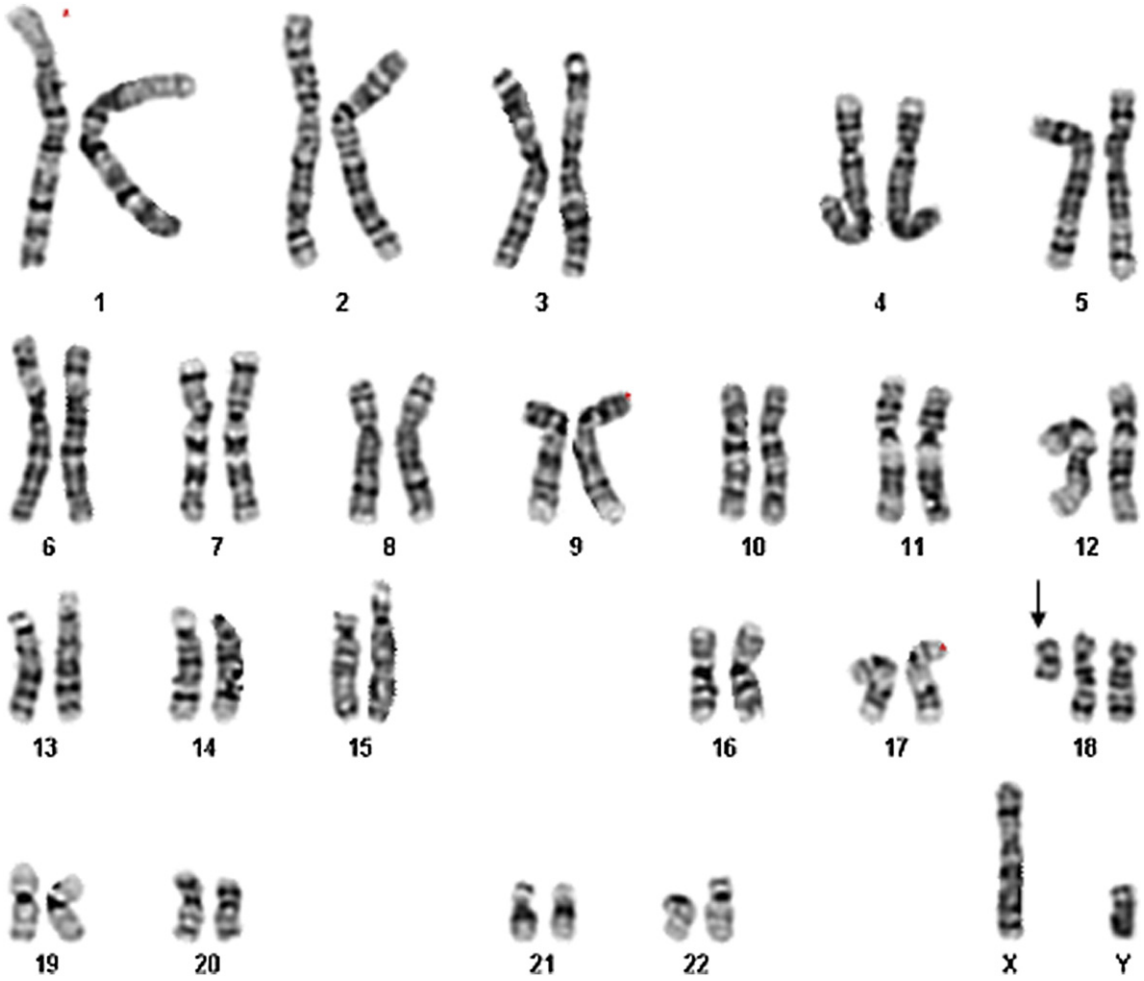

Fig. 1. The G-banded karyotype of 47,XY,+i(18)(p10). The arrow indicates a supernumerary isochromosome 18p.

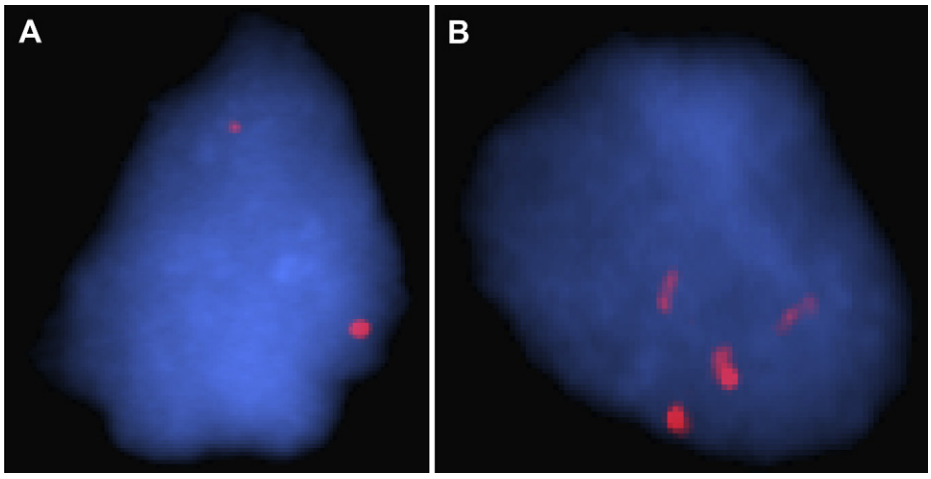

Fig. 2. Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes using an 18p11.32-specific probe RP11-324G2 (spectrum red) shows: (A) two red signals in a cell with disomy 18; (B) four red signals in a cell with a supernumerary isochromosome 18p.

blood, using chromosome 18-specific markers, showed biparental inheritance and, therefore, ruled out uniparental disomy for chromosome 18 (Fig. 3). When examined at 2 months of age, the infant was apparently normal, without phenotypic abnormalities, and had normal growth and development, although long-term follow-ups are required. Interphase FISH analysis on uncultured urinary cells, using an 18p11.32-specific probe (RP11-324G2) (spectrum red) and an 18q23-specific probe (RP11-154H12) (spectrum green), showed four red signals and two green signals in 9.4% (3/32 cells) of uncultured urinary cells and two red signals and two green signals in 90.6% (29/32 cells) of uncultured urinary cells (Fig. 4), indicating 9.4% mosaicism for tetrasomy 18p in the urinary system.

Discussion

Prenatal diagnosis of mosaic tetrasomy 18p is very rare. To date, at least seven cases of prenatally detected mosaic

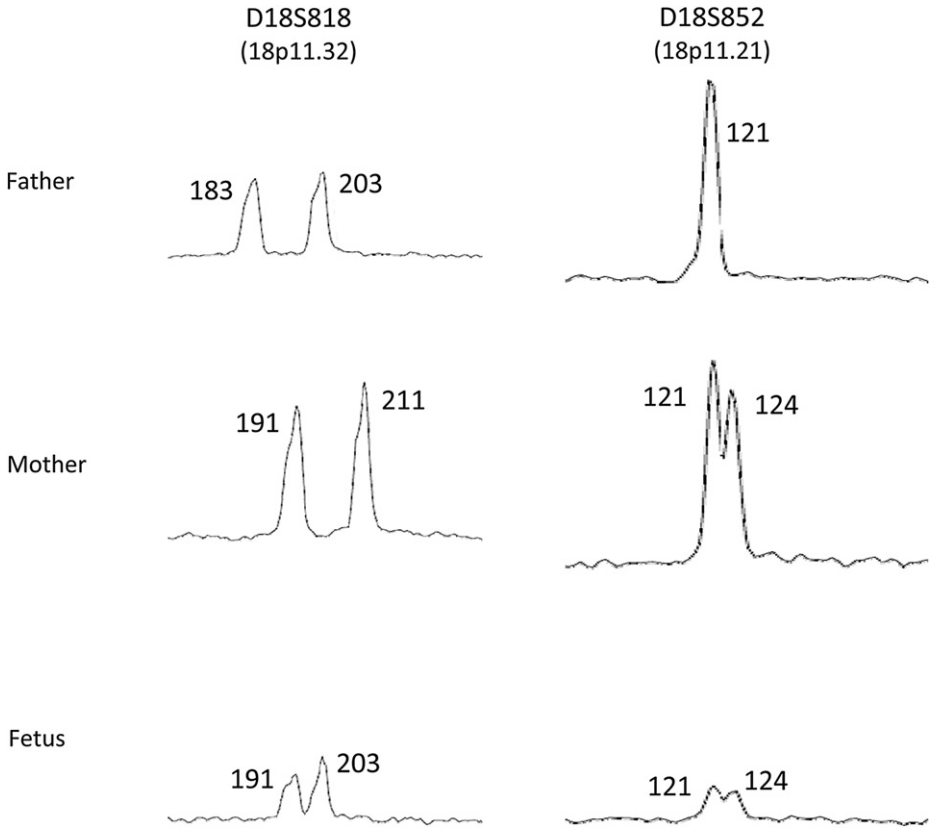

Fig. 3. Representative electrophoretogram of quantitative fluorescent polymerase chain reaction analysis on cord blood. The markers D18S818 (18p11.32) and D18S852 (18p11.21) show two peaks of equal fluorescent activity from two different parental alleles in the fetus and thus exclude uniparental disomy for chromosome 18.

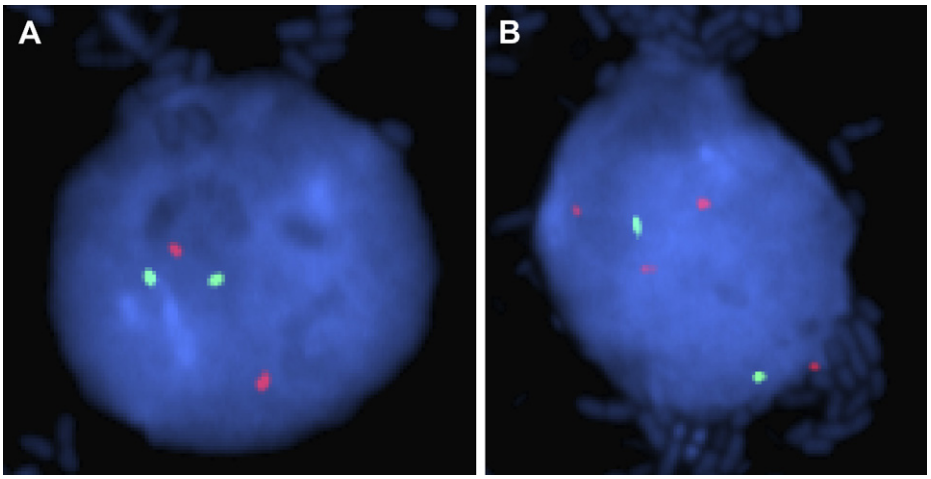

Fig. 4. Interphase FISH analysis on uncultured urinary cells using an 18p11.32-specific probe RP11-324G2 (spectrum red) and an 18q23-specific probe RP11-154H12 (spectrum green) shows: (A) two red signals and two green signals in a cell with disomy 18; (B) four red signals and two green signals in a cell with a supernumerary isochromosome 18p.

tetrasomy 18p have been described. Göcke et al [10] first reported prenatal diagnosis of mosaic tetrasomy 18p by amniocentesis, because of advanced maternal age. Amniocentesis at 16 weeks of gestation revealed 90% mosaicism (total 18 metaphases) for tetrasomy 18p. Repeated amniocentesis at 19 weeks of gestation revealed 75% mosaicism (total 20 metaphases) for tetrasomy 18p. The pregnancy was terminated. Postnatal analysis revealed a normal karyotype in lymphocytes, and placenta and mosaic tetrasomy 18p in the Achilles' tendon, skin, testis, kidney and lung, with mosaic levels of 28%, 40%, 50%, 50% and 50%, respectively. The abnormal male fetus manifested a small head, low-set ears, epicanthic folds, a pinched nose, high-arched palate, retrognathia, poorly formed philtrum, contracture of fingers, short broad hallux, hypoplastic penis, mile scoliosis and angulation of clavicles. Blennow et al [12] reported prenatal diagnosis of *de novo* mosaic tetrasomy 18p by amniocentesis, because of advanced maternal age. The pregnancy was terminated. The male abortus was normal. Hsu et al [13] reported two cases of mosaic tetrasomy 18p detected by amniocentesis. The first case had 73.5% (total 34 cells) mosaicism for tetrasomy 18p in amniocytes, and the mosaicism was confirmed. The female abortus was normal. The second case had 33.3% (total 27 cells) mosaicism for tetrasomy 18p in amniocytes. The cord blood had a karyotype of 46,XY. Mosaicism was confirmed in amnion, chorion and cord. The male liveborn was normal. Pinto et al [14] reported prenatal diagnosis of mosaic tetrasomy 18p by amniocentesis, because of advanced maternal age. Amniocentesis at 15 weeks of gestation revealed 50% mosaicism (total 32 cells) for tetrasomy 18p. The pregnancy was terminated. An abnormal female fetus was delivered with low-set posteriorly rotated ears, poorly formed philtrum, small upper lip, mild retrognathia, rocker-bottom feet, a short first toe, mitral valve dysplasia and excessive angulation in the left clavicle. Postnatal cytogenetic analysis revealed a normal karyotype in blood cells and 4% (4/103) mosaicism for tetrasomy 18p in the fibroblast cultures. Verschraegen-Spae et al [11] reported prenatal diagnosis of mosaicism of 47,XY,+mar/46,XY. The marker chromosome was confirmed to be i(18p). The pregnancy was terminated, and macroscopic and pathological examinations of the fetus were normal. Confirmation of i(18p) mosaicism in different fetal tissues, with different percentages of abnormal cells was as follows: blood (2.3%), placenta (3.4%), skin (7.1%), brain (7.1%), muscle (13.5%), lung (19.1%), testis (24%), kidney (26.5%) and liver (29.5%). Kim et al [15] reported prenatal diagnosis of *de novo* mosaic tetrasomy 18p in 35% (29/83 colonies) of cultured amniocytes at 20 weeks of gestation, because of advanced maternal age. The uncultured amniocytes were found to have an unusual skewed allele ratio at a single locus for 18p. Cord blood sampling at 23 weeks of gestation revealed a karyotype of 46,XY. Prenatal ultrasound showed normal findings, except for an absent cavum septum pellucidum. The parents opted to continue the pregnancy. A normal male baby was delivered with a normal karyotype in the cord blood. The newborn was healthy at 4 weeks of age. Postnatal ultrasound examinations of internal organs were normal, except for an absent cavum septum pellucidum.

Individuals with low-level mosaicism for tetrasomy 18p, may have offspring with tetrasomy 18p. For instance, Abeliovich et al [3] reported isochromosome 18p in a mother and her child. The woman had 3% mosaicism for tetrasomy 18p in the peripheral blood and was slightly dysmorphic but had normal development. Her daughter had a karyotype of 47,XX,+i(18p) and the full isochromosome 18p syndrome. Our case adds to the literature of low-level mosaicism for tetrasomy 18p detected prenatally, with an apparently normal phenotype.

The present case, along with our previous observations [16–20], has shown that interphase FISH on uncultured amniocytes is useful for rapid confirmation of mosaicism at amniocentesis. The present case provides evidence for karyotype discrepancy between amniocytes and fetal/neonatal blood in mosaic isochromosome 18p, as suggested by Kim

et al [15]. We suggest that interphase FISH analysis on uncultured amniocytes has the advantage of rapid positive confirmation of a supernumerary isochromosome 18p detected in cultured amniocytes by amniocentesis.

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