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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 11

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ABSTRACT

Objective: We present prenatal diagnosis and molecular cytogenetic characterization of a small supernumerary marker chromosome (sSMC) derived from chromosome 11.

Case report: A 37-year-old, gravida 3, para 2, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XX,+mar[18]/46,XX[4]. The parental karyotypes were normal. Level II ultrasound findings were unremarkable. Array comparative genomic hybridization (aCGH) on the DNA extracted from cultured amniocytes revealed no genomic imbalance. The sSMC was characterized by spectral karyotyping (SKY) using 24-color SKY probes and fluorescence *in situ* hybridization (FISH) using a whole chromosome paint (wcp) probe and a CEP11 (D11Z1) probe. The result was 47,XX,+mar.ish(11)(SKY+, wcp11+, D11Z1+)[16]/46,XX[4], indicating that the sSMC was derived from chromosome 11. A healthy female baby was delivered at 37 weeks of gestation with no phenotypic abnormalities. The cord blood had a karyotype of 47,XX,+mar[32]/46,XX[8]. Polymorphic DNA marker analysis of the blood excluded uniparental disomy 11. The female infant was normal in growth and psychomotor development during follow-ups at two months of age.

Conclusion: aCGH, SKY and FISH are useful in prenatal diagnosis of an sSMC derived from the centromeric region of a non-acrocentric chromosome.

Introduction

A small supernumerary marker chromosome (sSMC) has a size equal or smaller than that of chromosome 20 and cannot be identified or characterized its structural abnormalities by conventional cytogenetics [1]. Prenatally ascertained sSMCs occur in 0.075% of the cases at prenatal diagnosis [1–3] and have an overall 13% risk for phenotypic abnormalities [4]. An sSMC derived from a non-acrocentric chromosome has a 28% risk for phenotypic abnormalities comparing with a lower 7% risk in an sSMC derived from an acrocentric chromosome [5]. Liehr and Weise [6] additionally found that a prenatally ascertained sSMC derived from a

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non-acrocentric chromosome carries a 30% risk for phenotypic abnormalities.

We previously reported prenatal diagnosis of sSMC derived from non-acrocentric chromosomes with phenotypic abnormalities [7–9]. Here, we additionally report prenatal diagnosis of an sSMC derived from the centromeric region of chromosome 11 without phenotypic abnormalities.

Case report

A 37-year-old, gravida 3, para 2, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Cytogenetic analysis of cultured amniocytes revealed mosaicism for an sSMC and a karyotype of 47,XX,+mar[18]/46,XX[4]. Among 22 colonies of cultured amniocytes, 18 colonies had a

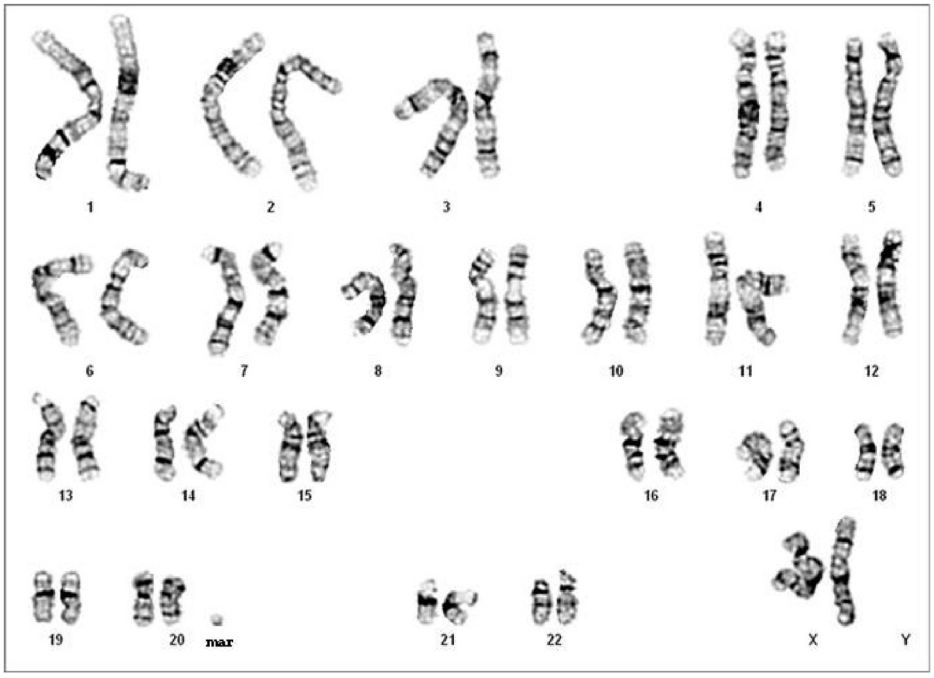

Fig. 1. A karyotype of 47,XX,+mar. mar = marker chromosome.

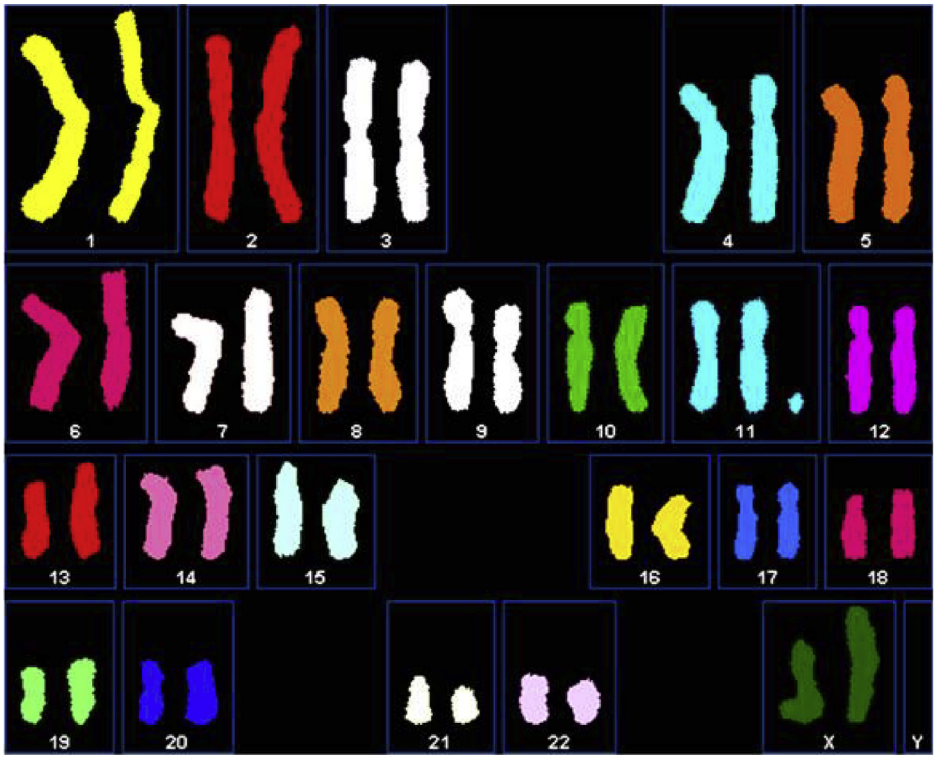

Fig. 2. Spectral karyotyping (SKY) using 24-color SKY probes demonstrates a small supernumerary marker chromosome derived from chromosome 11.

karyotype of 47,XX,+mar (Fig. 1), while the other four colonies had a karyotype of 46,XX. The parental karyotypes were normal. Level II ultrasound findings were unremarkable. Array comparative genomic hybridization (aCGH) on the DNA extracted from cultured amniocytes using CytoChip ISCA Array (Illumina, San Diego, CA, USA) revealed no genomic imbalance. The sSMC was characterized by spectral karyotyping (SKY) using 24-color SKY probes (Applied Spectral Imaging, Carlsbad, CA, USA) and fluorescence *in situ* hybridization (FISH) using Aquarius Whole Chromosome Painting Probe and Satellite Enumeration probes (Cytocell Inc. Adderbury, Oxfordshire, UK) containing a whole chromosome paint (wcp) 11 specific probe (green spectrum) and a CEP11 probe (red spectrum) corresponding to locus D11Z1 of chromosome 11. The result was 47,XX,+mar.ish(11)(SKY+, wcp11+, D11Z1+)[16]/46,XX[4], indicating that the sSMC was derived from chromosome 11 (Figs. 2 and 3). At 37 weeks of gestation, a healthy female baby was delivered with no phenotypic abnormalities. The cord blood had a karyotype of 47,XX,+mar[32]/46,XX[8]. Polymorphic DNA marker analysis on the DNAs obtained from the blood of the parents and the neonate excluded uniparental disomy 11. interphase FISH analysis of uncultured urinary cells obtained at the age four days using the probes of RP11-957F7 [11q11, fluorescein isothiocyanate (FITC), spectrum green] and RP11-209L12 (11q25, Texas Red, spectrum red) showed the marker cells in 25/44 (56.8%) of uncultured urinary cells (Fig. 4) comparing with 1/40 in the normal control. The female infant was normal in growth and psychomotor development during follow-ups at two months of age.

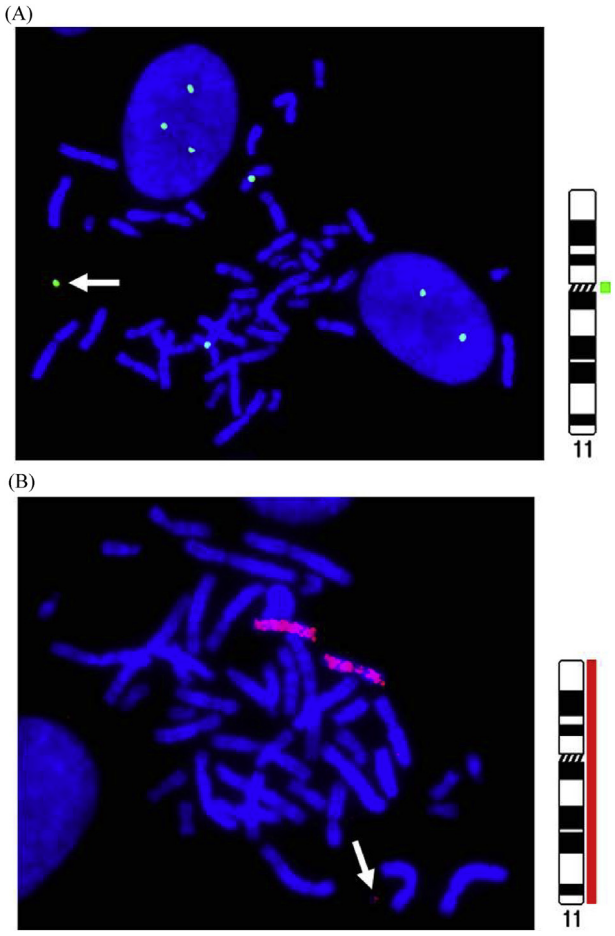

Fig. 3. Metaphase fluorescence *in situ* hybridization using (A) a CEP11 probe (spectrum green) corresponding to D11Z1 and (B) a whole chromosome paint 11 specific probe (spectrum red) shows a small supernumerary marker chromosome derived from chromosome 11. The arrow indicates the marker chromosome.

Discussion

Prenatal diagnosis of an sSMC derived from chromosome 11, or sSMC(11), is very rare. To date, at least seven cases of sSMC(11) without clinical findings and 10 cases of sSMC(11) with clinical findings have been reported [10]. Liehr [11] reported 47,XY,+mar [100%] in the blood of a 40-year-old male with bilateral testis hypoplasia. The sSMC was ascertained to be r(11)(::p11.12→q12.2::). Liehr [10] reported prenatal diagnosis of 47,XY,+mar[50%]/46,XY [50%] by amniocentesis because of advanced maternal age. The *de novo* sSMC was ascertained to be min(11)(:p11.1→q11:) by centromeric multicolor (cen M) and subcentromeric multicolor (subcen M) FISH. Prenatal ultrasound was normal, and postnatal follow-up showed normal status of the infant at age one month. Liehr [10] reported prenatal diagnosis of 47,XY,+mar[21]/46,XY[32] by amniocentesis because of advanced maternal age. The *de novo* sSMC was ascertained to be min(11)(:p11.1→q11:) by cen M and subcen M FISH. A normal child was born and was normal at age three months during follow-ups. Liehr [10] reported a normal female with

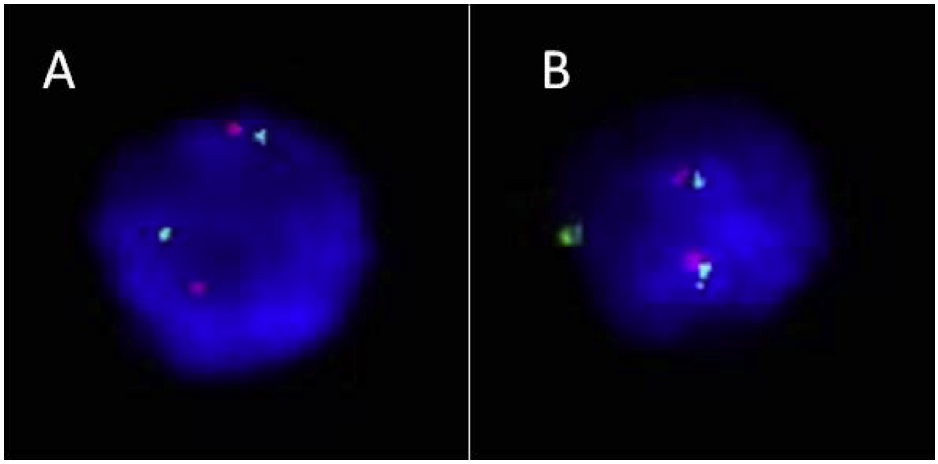

Fig. 4. Interphase fluorescence *in situ* hybridization analysis on uncultured urinary cells using the bacterial artificial chromosome probes of RP11-957F7 [11q11, fluorescein isothiocyanate (FITC), spectrum green] and RP11-209L12 (11q25, Texas Red, spectrum red) shows (A) a normal cell with two green signals and two red signals, and (B) a cell with the marker chromosome with three green signals and two red signals.

47,XX,+mar (100%). The sSMCs included r(11)(::p11.1→q12.2::)[10]/r(11)(::p11.1→q12.2::q12.2→p11.1:)[7]/min(11)(:q12.2→p11.1::p11.1→q12.2:)[3]. The woman had a 5-year-old daughter affected with developmental delay, muscular hypotonia and macrocephaly.

With the advent of aCGH, SKY and FISH, *de novo* non-acrocentric sSMCs can be well characterized by molecular cytogenetic techniques. We conclude that aCGH, SKY and FISH are helpful in genetic counseling of prenatally detected sSMC by providing immediate information on the origin and genetic content of the sSMC.

Conflicts of interest

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

Acknowledgments

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