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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 2

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ABSTRACT

Objective: We present prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome (sSMC) derived from chromosome 2.

Case Report: A 42-year-old woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+mar[10]/46,XY[12]. The parental karyotypes were normal. Array comparative genomic hybridization analysis of the DNA extracted from cultured amniocytes revealed no genomic imbalance. Spectral karyotyping analysis failed to identify the sSMC. Metaphase fluorescence *in situ* hybridization analysis using the satellite probes CEP1/5/19, CEP2, CEP3, CEP4, CEP6, CEP7, CEP8, CEP9, CEP10, CEP12, CEP13/21, CEP14/22, CEP15, CEP16, and CEP20 revealed a result of 47,XY,+mar .ish der(2)(D2Z+)[10]. The sSMC was derived from the α satellite of chromosome 2. Polymorphic DNA marker analysis using the markers specific for chromosome 2 on the DNAs extracted from cultured amniocytes and parental bloods excluded uniparental disomy 2. At 39 weeks of gestation, a healthy 3394-g male baby was delivered with no phenotypic abnormality. The cord blood had a karyotype of 47,XY,+mar[21]/46,XY[19].

Conclusion: Array comparative genomic hybridization and spectral karyotyping may fail to detect an sSMC derived from α satellite, which needs satellite probes for confirmation.

Introduction

We previously report prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome (sSMC) derived from r(2)(p11.1q21.2) with phenotypic abnormality [1]. Here, we additionally present prenatal diagnosis and molecular cytogenetic characterization of mosaicism

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for an sSMC derived from centric chromosome 2 with no phenotypic abnormality.

Case Report

A 42-year-old woman, gravida 3, para 1, underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+mar[10]/46,XY[12] (Figure 1). The parental karyotypes were normal. Array comparative genomic hybridization (aCGH) analysis of the DNA extracted from cultured amniocytes revealed no genomic imbalance. Spectral karyotyping (SKY) analysis failed to identify the sSMC. Metaphase fluorescence *in situ* hybridization analysis using the satellite probes CEP1/5/19, CEP2, CEP3, CEP4, CEP6, CEP7, CEP8, CEP9, CEP10, CEP12, CEP13/21, CEP14/22, CEP15, CEP16, and CEP20 (Cytocell, Adderbury, Oxfordshire, UK) revealed a result of 47,XY,+mar .ish der(2)(D2Z+)[10]. The sSMC was derived from the α satellite of chromosome 2 (Figure 2). Polymorphic DNA marker analysis by quantitative fluorescent polymerase chain reaction (QF-PCR) assays using the informative markers specific for chromosome 2 such as D2S423 (2p25.1) and D2S1325 (2p22.3) on the DNAs extracted from cultured amniocytes and parental bloods excluded uniparental disomy (UPD) 2 (Table 1). At 39 weeks of gestation, a healthy 3394-g male baby was delivered with no phenotypic abnormality. Cytogenetic analysis of the cord blood revealed a karyotype of 47,XY,+mar[21]/46,XY[19].

Discussion

Prenatal diagnosis of an sSMC(2) is very rare. The frequency of the sSMC in prenatal cases is 0.075% comparing with 0.044% in newborn cases, 0.288% in mentally retarded cases and 0.125% in subfertile cases [2]. About 72% of the sSMCs are derived from acrocentric chromosomes with the majority originated from chromosome 15 and the less frequent occurrence from chromosomes 13, 14, 21, and 22, and about 30% of the sSMCs are associated with euchromatic imbalance [2–4]. To date, at least 18 cases with prenatally detected sSMC(2) by amniocentesis have been reported [5]. Most reported cases with the sSMC(2) but without clinical findings are +der(2)(::p11.2 or p11.1→q11.1 or q11.2 or q12.1::) or CEP2(+), however, cases with +der(2)(::p11.2→q11.2::) or +der(2)(::p11.1→q12.1::) can be associated with phenotypic abnormality [5]. Therefore, a careful screening of ultrasound abnormality and a genetic investigation of UPD 2 are necessary in cases of prenatally detected centric sSMC(2). Prenatal diagnosis of an sSMC should require molecular cytogenetic investigation such as fluorescence *in situ* hybridization, aCGH, SKY, quantitative fluorescent polymerase chain reaction, and multicolor banding to determine the nature and the mosaic level of the sSMC, and to exclude UPD and the sSMC-related genetic syndromes such as Turner syndrome, marker chromosome 15 syndrome, supernumerary der(22)t(11;22) syndrome, cat-eye syndrome, der(22)t(8;22)(q24.1;q11.1) syndrome, isochromosome i(5p) syndrome, 9p isochromosome syndrome, tetrasomy 15qter syndrome, isochromosome 12p or Pallister–Killian syndrome, isochromosome 15q12 syndrome, isochromosome 18p syndrome, derivative-8 syndrome and derivative-13/21 syndrome [2,6].

The sSMC has been associated with human infertility. Manvelyan et al [7] found an sSMC rate of 0.125% in patients with fertility problems and an sSMC rate of 7% in males with decreased sperm parameters. Manvelyan et al [7] also observed one male and one female patients with mosaicism for sSMC(2) or r(2)(::p11.1→q11.2::) and fertility problems. Olszewska et al [8] suggested a genetic dosage and position effect of sSMC in human nuclei in infertile male patients. Olszewska et al [8] observed significant repositioning of X and Y chromosomes towards the nuclear periphery and both X and Y chromosomes being close to the sSMC, and suggested the effect of sSMC/XY colocalization on meiotic chromosome division and the consequence of abnormal chromosome segregation. Armanet et al [4] suggested a gene dosage increase effect as well as mechanical effects perturbing meiosis of sSMC on human infertility.

In summary, we present prenatal diagnosis and molecular cytogenetic characterization of mosaicism for an sSMC(2). Our

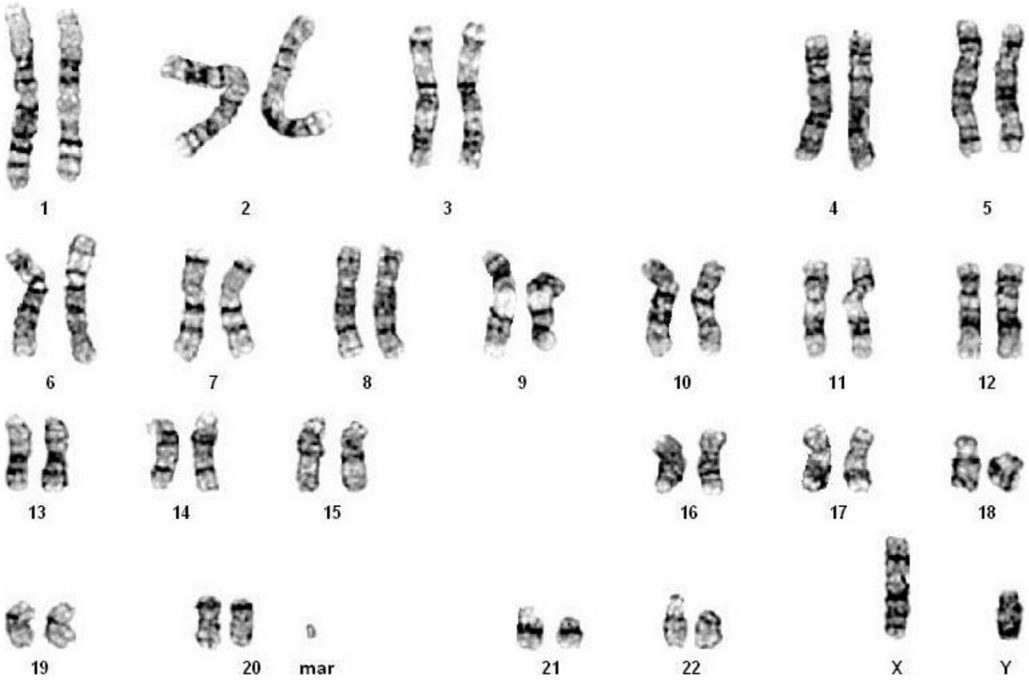

Figure 1. A karyotype of 47,XY,+mar. mar = marker chromosome.