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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from 2q11.1-q12.1 associated with fetal bilateral radial dysplasia

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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 2q11.1-q12.1 associated with fetal bilateral radial dysplasia.**Case report:** A 27-year-old woman underwent amniocentesis at 18 weeks of gestation because of club hands on fetal ultrasound. The internal organs of the fetus were normal. Amniocentesis revealed a karyotype of 47,XY,+mar [13]/46,XY [11]. The parental karyotypes were normal. Simultaneous array comparative genomic hybridization (aCGH) analysis of the DNA extracted from uncultured amniocytes revealed the result of arr 2q11.1q12.1 (95,529,039–102,825,556) × 3.0 [GRCh37 (hg19)]. The pregnancy was terminated at 20 weeks of gestation, and a malformed fetus was delivered with isolated bilateral radial dysplasia. The cord blood had a karyotype of 47,XY,+mar[24]/46,XY[16]. Polymorphic DNA marker analysis of the DNAs extracted from umbilical cord and parental bloods excluded uniparental disomy for chromosome 2. Metaphase fluorescence *in situ* hybridization analysis confirmed an sSMC derived from chromosome 2q11.1-q12.1 in cultured amniocytes.**Conclusion:** High-level mosaicism for an sSMC derived from chromosome 2q11.1-q12.1 can be associated with fetal abnormalities.© 2020 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

We previously reported prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome (sSMC) derived from chromosome 2 [1,2]. Here, we present an additional case derived from 2q11.1-q12.1 associated with fetal bilateral radial dysplasia.

Case report

A 27-year-old, primigravid woman underwent amniocentesis at 18 weeks of gestation because of club hands on fetal ultrasound. The internal organs of the fetus were normal. The woman did not have diabetes mellitus and did not take any teratogenic medicine during this pregnancy. Her husband was 30 years old, and there was no family history of congenital malformations. Amniocentesis revealed a karyotype of 47,XY,+mar [13]/46,XY [11] (Fig. 1). The parental karyotypes were normal. Simultaneous array comparative genomic hybridization (aCGH) analysis of the DNA extracted from uncultured amniocytes revealed the result of arr 2q11.1q12.1 (95,529,039–102,825,556) × 3.0 [GRCh37 (hg19)] with a 7.297-Mb

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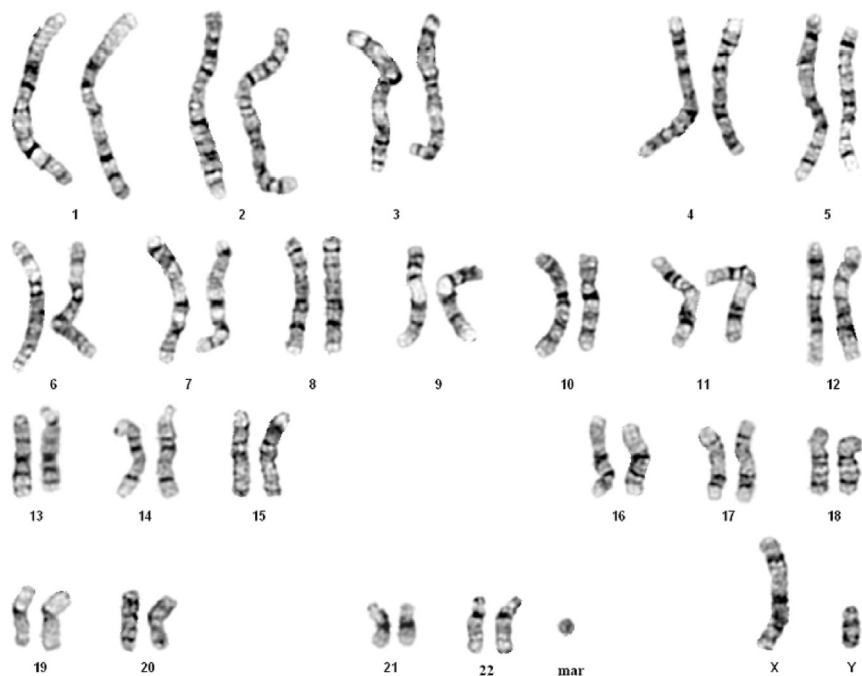


Fig. 1. A karyotype of 47,XY,+mar. mar = marker chromosome.

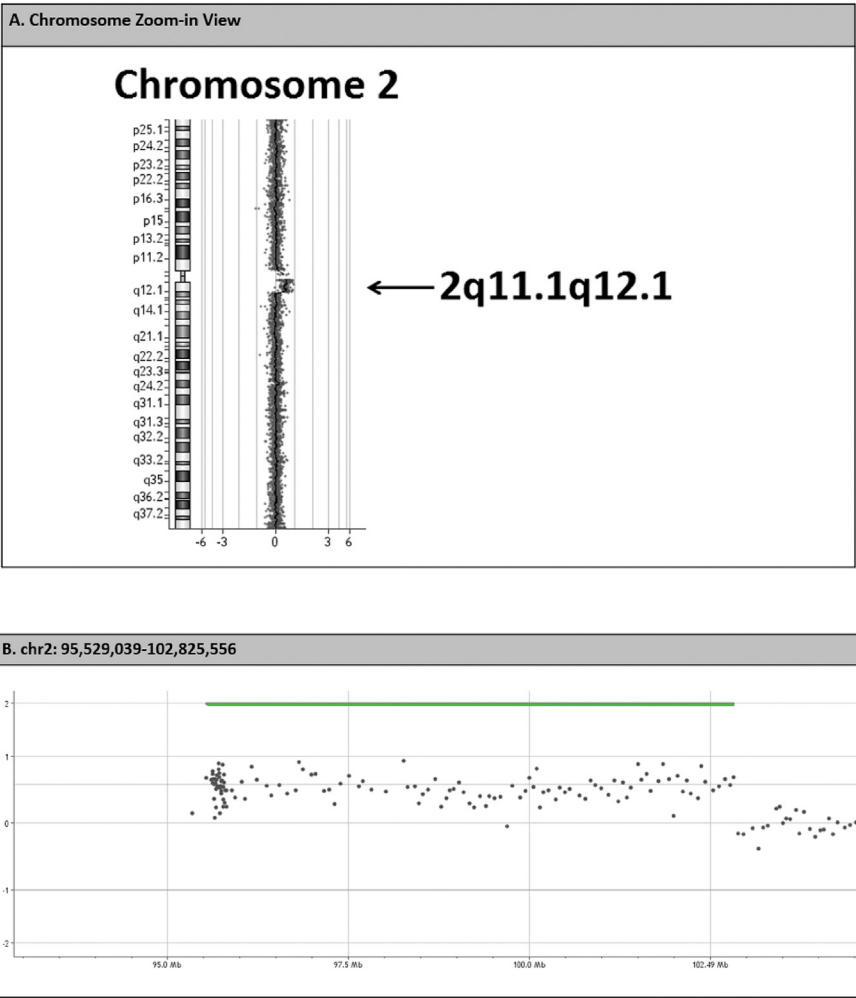


Fig. 2. (A) and (B) Array comparative genomic hybridization analysis using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K (Agilent Technologies, Santa Clara, CA, USA) shows the result of arr 2q11.1q12.1 (95,529,039–102,825,556) × 3.0 [GRCh37 (hg19)] with a 7.297-Mb gene dosage increase at 2q11.1–q12.1.

(A)



(B)

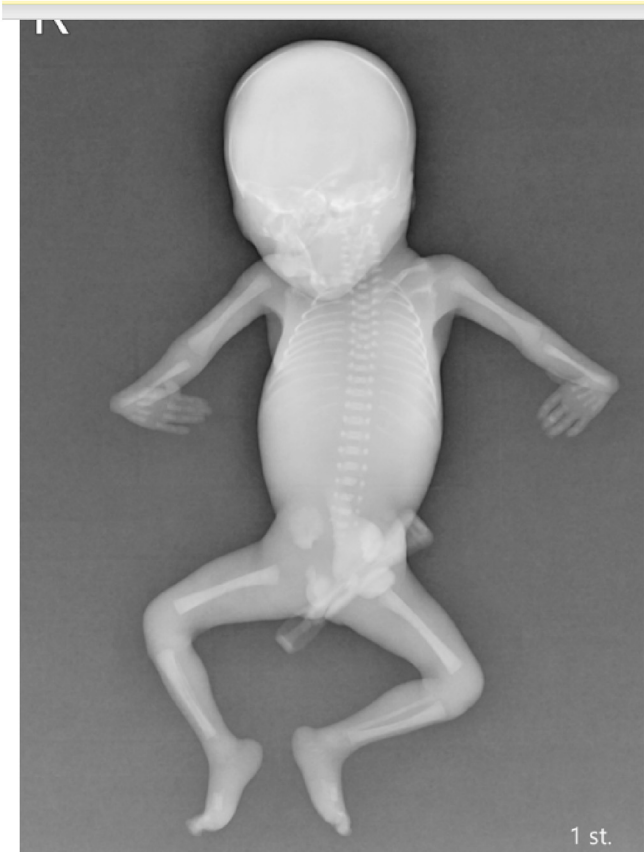


Fig. 3. (A) The fetus with bilateral radial dysplasia and (B) the skeletal radiographic finding.

gene dosage increase at 2q11.1–q12.1 encompassing 49 Online Mendelian Inheritance in Man (OMIM) genes (Fig. 2). The pregnancy was terminated at 20 weeks of gestation, and a malformed fetus was delivered with isolated bilateral radial dysplasia (Fig. 3). The cord blood had a karyotype of 47,XY,+mar[24]/46,XY[16]. Polymorphic DNA marker analysis of the DNAs extracted from umbilical cord and parental bloods excluded uniparental disomy for chromosome 2 (Fig. 4). Metaphase fluorescence *in situ* hybridization (FISH) analysis confirmed an sSMC derived from 2q11.1–q12.1 in cultured amniocytes (Fig. 5).

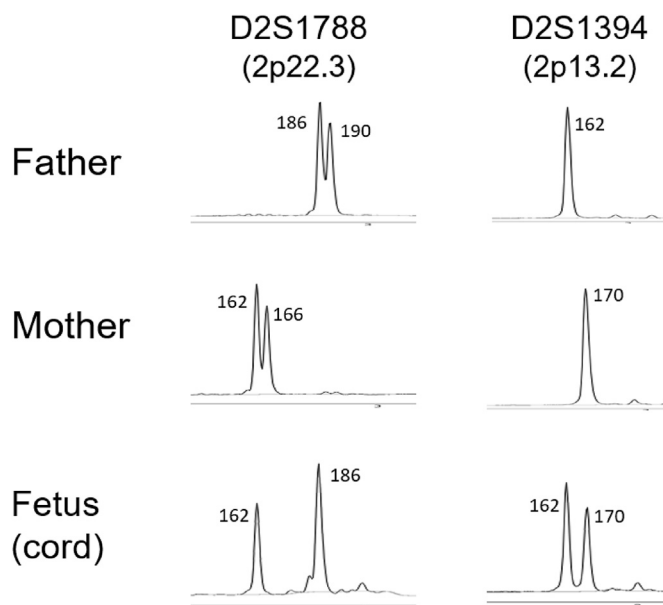


Fig. 4. Polymorphic DNA marker analysis on the DNAs extracted from umbilical cord and parental bloods using the informative markers of D2S1788 (2p22.3) and D2S1394 (2p13.2) shows biparental alleles in the umbilical cord.

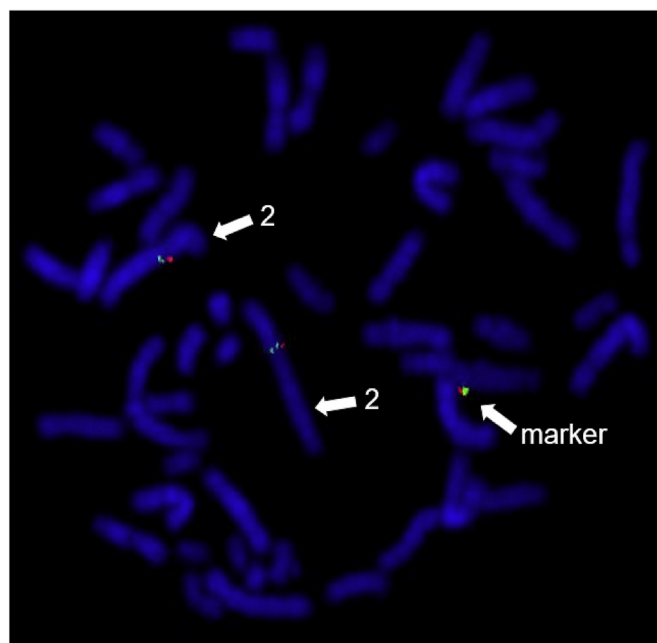


Fig. 5. Metaphase fluorescence *in situ* hybridization analysis on cultured amniocytes using the bacterial artificial chromosome (BAC) probes of RP11-765E3 [2q11.1; fluorescein isothiocyanate (FITC), spectrum green] and RP11-759O11 (2q12.1; Texas Red, spectrum red) shows that the supernumerary marker chromosome (sSMC) contains one red signal and one green signal, consistent with an sSMC derived from chromosome 2q11.1–q12.1.

Discussion

The present case had mosaicism for an sSMC in 54.2% of cultured amniocytes and in 60% of cultured cord blood lymphocytes, and aCGH analysis on the DNA extracted from uncultured amniocytes showed a 7.297-Mb duplication of 2q11.1–q12.1. Prenatal diagnosis of an sSMC derived from chromosome 2q11.1–q12.1 is very rare. To our knowledge, only one case has been reported [3]. Marle et al. [3] reported prenatal diagnosis of 47,XY + mar[20]/46,XY [10] at amniocentesis in a pregnancy at 28 weeks of gestation with fetal ventricular and atrial septal defects and coarctation of aorta, and an 8.57-Mb duplication of 2q11.1–q12.1 or arr 2q11.1q12.1 (94,894,358–103,466,335) × 3 (hg18). The pregnancy was subsequently terminated, and a fetus was delivered with facial dysmorphism and congenital heart defects.

To date, at least six cases with an sSMC derived from chromosome 2 encompassing 2q11.1–q12.1 have been reported in postnatal peripheral blood analysis. Among these six postnatal cases, five cases were associated with clinical findings, and one case with unclear clinical correlation. Liehr [4] reported a 10-day-old newborn with a karyotype of 47,XX,+mar[30]/46,XX [8]dn at peripheral blood analysis and an sSMC derived from min(2)(:p11.1→q11.2–q12.1:) determined by FISH and CGH. The baby was associated with facial dysmorphism, situs inversus, dextrocardia, ventricular septal defect and bilateral duplication of the renal collecting system. Liehr [4] reported a 2-year-old female with a karyotype of 47,XX,+mar [7]/46,XX[43]dn at peripheral blood analysis and an sSMC derived from min(2)(:p11.1→q11.2–q12.1:) determined by aCGH. The baby was associated with hypotonia, seizures, globulous kidneys, facial dysmorphism and microcephaly. Baldwin et al. [5] reported a postnatal case with mosaic 48,XX,+mar,+mar in 10%, 47,XX,+mar in 45% and 46,XX in 45% at peripheral blood analysis and an sSMC derived from r(2)(::p11.1→q12.1::) with a size of 9 Mb determined by aCGH. The proband had cleft palate, language learning delay and mild dysmorphism. Liehr [4] reported a 7-year-old male with a karyotype of 47,XY,+mar[20]/46,XY [10] at peripheral blood analysis and an sSMC derived from r(2)(::p11.1→q12.1::). The patient had developmental delay and seizures. Kuuse et al. [6] reported a 3-year-old male with mosaic 47,XY,+mar in 70% and 46,XY in 30% at peripheral blood analysis and an sSMC derived from r(2)(::p11.1→q12.1::) determined by aCGH. The patient had developmental delay, dysmorphism and microcephaly. Jang et al. [7] reported a 2-month-old male with karyotype of 47,XY,+mar [8]/46,XY[42] at peripheral blood analysis and an sSMC derived from mar(2)(:p11.1→q12.1:) and an aCGH result of arr(hg19) 2q11.1q12.1 (95,529,039–105,358,887) × 3. The patient had prematurity, developmental delay and atrial septal defect. Our case and a literature review of other seven reported cases provide evidence that high-level mosaicism for an sSMC derived from 2q11.1→q12.1 is likely to be associated with phenotypic abnormalities.

The peculiar aspect of the present case is the prenatal diagnosis of an sSMC derived from chromosome 2 because of a prenatal ultrasound finding of isolated bilateral radial dysplasia. Mancuso et al. [8] reported prenatal diagnosis of isolated bilateral radial dysplasia at 20 weeks of gestation in a fetus with a karyotype of 46,XY. Radial dysplasia or hypoplasia is very rare and occurs in 1:6000 to 8000 live births [9]. Prenatal diagnosis of radial dysplasia should include a differential diagnosis of syndromic radial dysplasia such as VACTERL association (vertebral defects, anal

atresia, cardiac defects, tracheoesophageal fistula, renal abnormalities and limb abnormalities), Fanconi anemia, Holt-Oram, TAR (thrombocytopenia-absent radius), Townes-Brocks, Baller-Gerold, Rothmund-Thompson, RAPADILINO, Duane-radial ray (Okhiro), IVIC and lacrimo-auriculo-dento-digital (LADD) syndromes [9–12]. However, none of the above syndromic radial dysplasia has been associated with genes located at 2q11.1–q12.1. In addition to syndromic radial dysplasia, aneuploidy (trisomies 13 and 18), diabetic embryopathy, teratogens of valproate, ectrodactyly and amniotic band syndrome can also be associated with radial dysplasia [13].

In summary, we present prenatal diagnosis and molecular cytogenetic characterization of mosaicism for an sSMC derived from 2q11.1–q12.1 associated with fetal bilateral radial dysplasia. Our presentation and a review of the literature show that high-level mosaicism for an sSMC derived from chromosome 2q11.1–q12.1 can be associated with fetal abnormalities.

Declaration of competing interest

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

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