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## Case Report

## Prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 3

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## ABSTRACT

**Objective:** We present prenatal diagnosis and molecular cytogenetic characterization of a small supernumerary marker chromosome (sSMC) derived from chromosome 3.**Case report:** A 36-year-old woman underwent amniocentesis at 19 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XX,+mar[6]/46,XX[18]. The mother's karyotype was 47,XX,+mar[4]/46,XX[46]. The father's karyotype was 46,XY. Array comparative genomic hybridization (aCGH) analysis of uncultured amniocytes revealed a result of arr 3q11.1q12.1 (93,575,285–98,956,687) × 2–3 [GRCh37 (hg19)]. Prenatal ultrasound findings were unremarkable. The parents elected to continue the pregnancy, and a 2470-g female baby was delivered at 37 weeks of gestation without phenotypic abnormalities. The cord blood had a karyotype of 47,XX,+mar[8]/46,XX[32]. aCGH analysis of cord blood revealed a result of arr 3q11.1q12.2 (93,649,973–97,137,764) × 2.4 [GRCh37 (hg19)] with a log2 ratio of 0.25 and a 30–40% mosaicism for 3.488-Mb dosage increase in 3q11.1–q11.2 encompassing four [Online Mendelian Inheritance in Man (OMIM)] genes of *PROS1*, *ARL13B*, *NSUN3* and *EPHA6*. Metaphase fluorescence *in situ* hybridization (FISH) analysis confirmed 30% (6/20 cells) mosaicism for the sSMC(3) in the blood lymphocytes.**Conclusion:** aCGH and FISH analyses are useful for perinatal investigation of a prenatally detected sSMC.© 2019 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

A small supernumerary marker chromosome (sSMC) is defined as a marker chromosome that has a size equal to or smaller than that of chromosome 20 and cannot be characterized by conventional cytogenetic technology [1]. An sSMC occur in 0.075% of the

cases at prenatal diagnosis [1–3]. An sSMC has a 13% overall risk for phenotypic abnormalities [4]. There is a significant difference in the risk for phenotypic abnormalities between the sSMC derived from a non-acrocentric chromosome and the sSMC derived from an acrocentric chromosome (28% vs. 7%) [5]. In fact, an sSMC derived from a non-acrocentric chromosome has been found to carry a 30% risk for phenotypic abnormalities [6].

With the advent of modern genetic technologies, molecular cytogenetic characterization of an sSMC derived from a non-acrocentric chromosome [7–10], or an acrocentric chromosome [11] at prenatal diagnosis has been well described. Here, we present

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prenatal diagnosis and molecular cytogenetic characterization of an sSMC derived from chromosome 3 in a pregnancy with a favorable outcome.

### Case Report

A 36-year-old, gravida 2, para 1, woman underwent amniocentesis at 19 weeks of gestation because of advanced maternal age. Her husband was 37 years old, and there was no history of congenital malformations in the family. Amniocentesis revealed a karyotype of 47,XX,+mar[6]/46,XX[18]. Among 24 colonies of cultured amniocytes, six colonies had an sSMC, whereas the other 18 colonies had a normal karyotype. Simultaneous array comparative genomic hybridization (aCGH) analysis by International Standard Cytogenomic Array Consortium (ISCA) oligonucleotide array 60 K on the DNA extracted from uncultured amniocytes showed a result of arr 3q11.1q12.1 (93,575,285–98,956,687)  $\times$  2–3 [GRCh37 (hg19)]. There was a 5.4-Mb partial gene dosage increase in 3q11.1–q12.1. Cytogenetic analysis of parental bloods showed a karyotype of 47,XX,+mar [4]/46,XX[46] in the mother and a karyotype of 46,XY in the father. Prenatal ultrasound findings were unremarkable. The parents elected to continue the pregnancy, and a 2470-g female baby was delivered at 37 weeks of gestation without phenotypic abnormalities. Cytogenetic analysis of the cord blood revealed a karyotype of 47,XX,+mar[8]/46,XX[32] (Fig. 1). aCGH analysis using CytoScan 750 K Array (Affymetrix, Santa Clara, CA, USA) on the DNA extracted from cord blood showed a result of arr 3q11.1q11.2 (93,649,973–97,137,764)  $\times$  2.4 [GRCh37 (hg19)] with a log<sub>2</sub> ratio of 0.25 and a 30–40% mosaicism for 3.488-Mb dosage increase in 3q11.1–q11.2 encompassing four [Online Mendelian Inheritance in Man (OMIM)] genes of *PROS1*, *ARL13B*, *NSUN3* and *EPHA6* (Fig. 2). Metaphase fluorescence *in situ* hybridization (FISH) analysis confirmed a 30% (6/20 cells) mosaicism for the sSMC(3) in the blood lymphocytes (Fig. 3). Repeat cytogenetic analysis of maternal blood revealed a karyotype of 46,XX in 40/40 lymphocytes, and aCGH analysis of maternal blood revealed a result of arr (1–22, X)  $\times$  2, Y $\times$ 0. No genomic imbalance could be detected in the maternal blood. Interphase

FISH analysis of maternal blood lymphocytes showed normal signals in 64/64 cells. The female infant was doing well at the age of two years.

### Discussion

To date, at least 33 cases with sSMC(3) have been reported, of which 23 cases (23/33 = 70%) had no clinical findings, whereas 10 cases (10/33 = 30%) had clinical findings [12]. Most cases of sSMC(3) with clinical findings had the involvement of 3p12. Rothmund et al. [13] reported a 1-year-old female who had a karyotype of 47,XX,+r[70%]/46,XX[30%]dn with the sSMC of r(3)(::p10→q11::), slight dysplastic features, muscular hypotonia and feeding difficulties but normal psychomotor development. Anderlid et al. [14] reported an 8-year-old female who had a karyotype of 47,XX,+r[4]/46,XX[16]dn with the sSMCs of r(3)(::p12→q13.2::)[12%] and r(3)(::p12→q13.2::p12→q13.2::)[12%], mild developmental delay, short stature, Turner syndrome phenotype and slow language. Yu et al. [15] reported 47,XX,+mar [100%]dn at amniocentesis in a fetus with the sSMC of min(3)(:p12.1→q11.2:), intrauterine growth restriction, oligohydramnios and fetal dolichocephaly. Yu et al. [16] reported a 5-year-old male who had a karyotype of 47,XY,+r[11]/46,XY[9]dn with the sSMC of r(3)(:p12.3→q11.2:), global developmental delay, sagittal craniosynostosis, facial dysmorphism, patent ductus arteriosus, scoliosis, small phallus and clinodactyly. Liehr [17] reported 47,XX,+mar [16]/46,XX[33] at amniocentesis with the sSMCs of dic(3)(:p12.1→q11.2::q11.2→p12.1:)[12]/min(3)(:p12.1→q11.2:)[3]/r(3)(:p12.1→q11.2:)[1], developmental retardation at age eight years, microcephaly, seizures and no language in the patient.

An sSMC(3) may be associated with uniparental disomy (UPD) 3. Srebnik et al. [18] reported maternal UPD 3 in a fetus with 47,XX,+mar[100%] and the sSMC of min(3)(:p12.2→q10:), but no phenotypic abnormalities. To date, no phenotypic abnormalities specific to paternal UPD 3 [19] or maternal UPD 3 [20] have been reported. It is suggested that there is an absence of maternally imprinted genes and paternally imprinted genes on chromosome 3 [19,20]. The reported disorders in patients with UPD 3 are limited to autosomal recessive diseases such as Pierson syndrome [21], dystrophic epidermolysis bullosa [Fassihi et al., 2006], GM1 gangliosidosis [22,23] and Fanconi-Bickel syndrome [24].

The present case had a gene dosage increase in 3q11.1–q11.2 encompassing the genes of *PROS1*, *ARL13B*, *NSUN3* and *EPHA6*. *PROS1* (OMIM 176880) encodes protein S, and mutations or deletions in *PROS1* have been associated with autosomal dominant thrombophilia due to protein S deficiency (OMIM 612336) [25–28] and autosomal recessive thrombophilia due to protein S deficiency (OMIM 614514) [29,30]. *ARL13B* (OMIM 608922) encodes ADP-ribosylation factor-like 13B of small GTPases of the RAS superfamily, and mutations of *ARL13B* are associated with autosomal recessive Joubert syndrome 8 (OMIM 612291), which is characterized by ciliopathy of molar tooth sign and superior vermian dysplasia [31,32]. *NSUN3* (OMIM 617491) encodes a mitochondrial protein of S-adenosylmethionine-dependent 5-methylcytosine (m5C) methyltransferase. Loss-of-function of *NSUN3* mutations has been associated with deficient methylation and formylation of mt-tRNA(Met) wobble cytosine in a patient with mitochondrial disease [33]. *EPHA6* (OMIM 600066) encodes an Eph receptor.

In summary, we present prenatal diagnosis and molecular cytogenetic characterization of an sSMC derived from chromosome 3. Our case shows that an sSMC(3) with the involvement of 3q11.1–q11.2 can be associated with a favorable outcome, and aCGH and

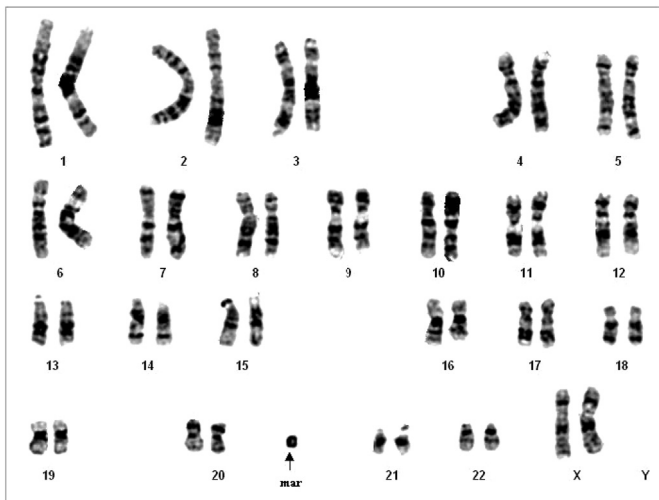
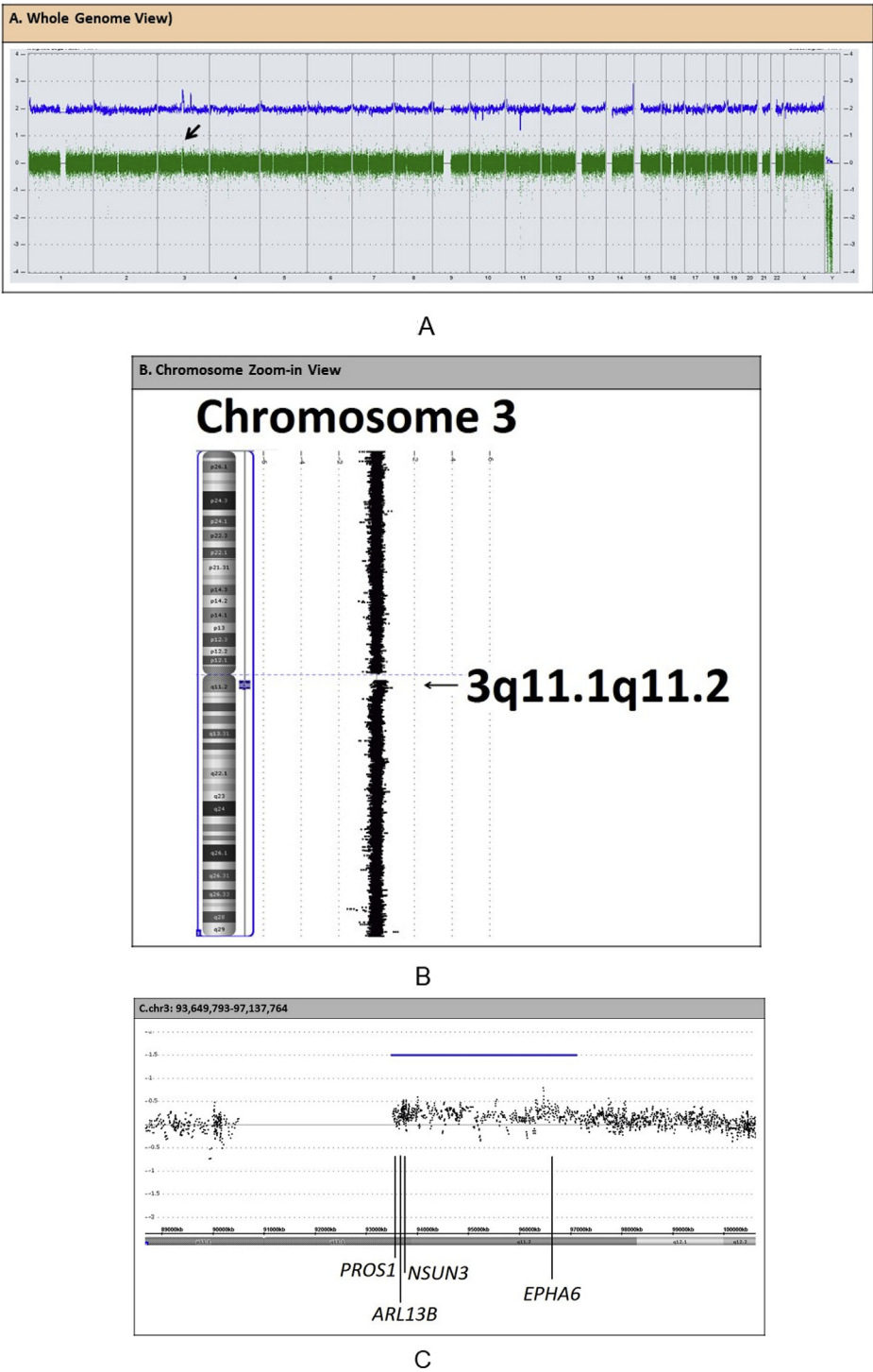
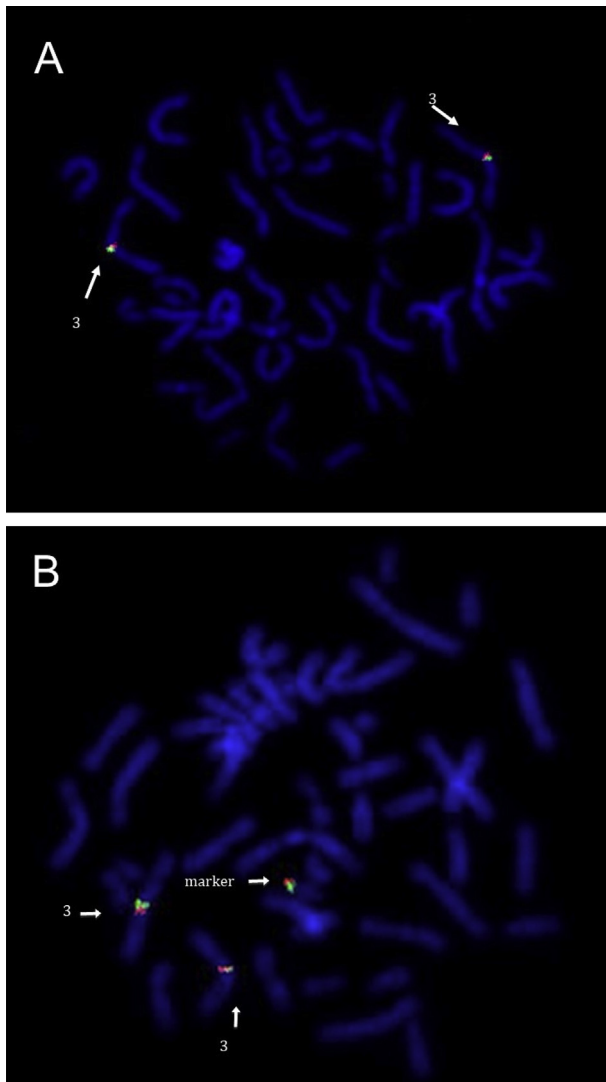


Fig. 1. A karyotype of 47,XX,+mar. The arrow indicates a marker chromosome (mar).



**Fig. 2.** (A), (B) and (C) Array comparative genomic hybridization on the DNA extracted from cord blood shows a 30–40% ( $\log_2$  ratio = 0.25) 3.488-Mb gene dosage increase in 3q11.1q11.2 encompassing the genes of *PROS1*, *ARL13B*, *NSUN3* and *EPHA6*.



**Fig. 3.** Metaphase fluorescence *in situ* hybridization analysis on cord blood lymphocytes by the bacterial artificial chromosome probes of RP11-945N7 [3q11.2; spectrum green, fluorescein isothiocyanate (FITC)] and RP11-976N14 (3q11.2; spectrum red, Texas Red) shows (A) a normal chromosome 3 with two green-red signals and (B) a marker chromosome with three green-red signals.

FISH are useful for perinatal investigation of a prenatally detected sSMC.

### Conflicts of interest

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

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