Prenatal Diagnosis and Molecular Cytogenetic Characterization of a Small Supernumerary Marker Chromosome Derived From Chromosome 18 and Associated With a Reciprocal Translocation Involving Chromosomes 17 and 18

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SUMMARY

Objective: Prenatal diagnosis of small supernumerary marker chromosomes (sSMC) gives rise to difficulties in genetic counseling, and requires molecular cytogenetic technologies such as spectral karyotyping, fluorescence *in situ* hybridization, multicolor-fluorescence *in situ* hybridization, or array-comparative genomic hybridization to identify the nature of the aberrant chromosome. We report such a case associated with a reciprocal translocation.

Materials, Methods and Results: A 36-year-old woman, gravida 7, para 1, abortus 5, was referred for amniocentesis at 18 weeks of gestation because of advanced maternal age. Amniocentesis revealed a reciprocal translocation between chromosomes 17q and 18q and an sSMC. The karyotype was 47,XY,t(17;18)(q11.1;q11.2), +mar. Chromosome preparations from blood lymphocytes revealed that she had the same reciprocal translocation and sSMC. Spectral karyotyping showed that the sSMC was derived from the centromeric region of chromosome 18, and there was a reciprocal translocation between chromosomes 17 and 18. The derivative chromosome 17 had positive 17p terminal (17pTEL) and chromosome 17 centromeric (cep17) signals but did not have a positive chromosome 18 centromeric signal (cep18). The derivative chromosome 18 had positive 18p terminal (18pTEL), chromosome 18 centromeric (cep18) and cep17 signals. The sSMC had only a positive cep18 signal. These findings suggested that a breakpoint occurred at 17q11.1 and another at 18q11.2 during translocation, and the sSMC originated from chromosome 18. The karyotype of the fetus was thus 47,XY,t(17;18)(q11.1;q11.2), +mar.ish der(17)t(17;18)(q11.1;q11.2)(17pTEL+,D17Z1+),der(18)t(17;18)(q11.1;q11.2)(18pTEL+,D18Z1+,D17Z1+), + der(18)(D18Z1+). Oligonucleotide-based array comparative genomic hybridization demonstrated no gain or loss of the gene dosage on chromosomes 17 and 18.

Conclusion: Our case adds to the reported cases of sSMCs derived from the centromeric region of chromosome 18 without phenotypic consequences. [*Taiwan J Obstet Gynecol* 2010;49(2):188–191]

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Introduction

Prenatal diagnosis of small supernumerary marker chromosomes (sSMCs) results in difficulties with respect to genetic counseling, and requires molecular cytogenetic technologies such as spectral karyotyping (SKY), fluorescence *in situ* hybridization (FISH), multicolor-FISH (M-FISH), centromere-specific multicolor-FISH (cenM-FISH) and subcentromeric multicolor-FISH (subcenM-FISH), or array comparative genomic hybridization (aCGH) to identify the nature of the aberrant chromosome [1–4]. sSMCs are defined as structurally abnormal chromosomes that cannot be identified or characterized by conventional banding cytogenetics and are generally equal in size or smaller than chromosome 20 [5–7]. sSMCs are present in 0.044% of newborn infants and in 0.075% of prenatal cases [4,5,7,8]. About 70% of sSMCs arise *de novo* [8], around 70% of sSMCs are derived from acrocentric chromosomes [5,9], and approximately 70% of cases from *de novo* sSMCs have no phenotypic effects [4].

Materials, Methods and Results

A 36-year-old woman, gravida 7, para 1, was referred for amniocentesis at 18 weeks of gestation because of advanced maternal age. The woman was phenotypically normal but had experienced five spontaneous abortions and delivered a phenotypically normal son. Amniocentesis revealed a reciprocal translocation between chromosome arms 17q and 18q and a sSMC. The karyotype was 47,*XY*,t(17;18)(q11.1;q11.2),+mar (Figure 1). Chromosome preparations of blood lymphocytes from the woman revealed that she had the same reciprocal translocation and sSMC. At 38 weeks of gestation, the woman delivered a healthy 2,656 g male baby without any phenotypic abnormality. The sSMC and the derivative chromosome were characterized by SKY using 24-color SKY probes (Applied Spectral Imaging, Carlsbad, CA, USA) and FISH using a 17p-specific telomeric probe (17pTEL), chromosome 17 centromeric probe (cep17), 18p-specific telomeric probe (18pTEL), and chromosome 18 centromeric probe (cep18) (TelVysion; Vysis, Downers Groove, IL, USA). SKY showed that the sSMC was derived from the centromeric region of chromosome 18, and there was a reciprocal translocation between chromosomes 17 and 18 (Figure 2). The derivative chromosome 17, der(17), had positive 17pTEL and cep17 signals (Figure 3) but did not have a positive cep18 signal (Figure 4). The derivative chromosome 18, der(18), had positive 18pTEL and cep18 signals (Figure 4) and a positive cep17 signal (Figure 3). The sSMC had only a positive cep18 signal (Figure 4). These findings suggested that a breakpoint occurred at 17q11.1 and another at 18q11.2 during translocation, and the sSMC originated from chromosome 18. The karyotype of the fetus was thus 47,*XY*, t(17;18)(q11.1;q11.2),+mar.ish der(17)t(17;18)(q11.1;q11.2)(17pTEL+, D17Z1+),der(18)t(17;18)(q11.1;

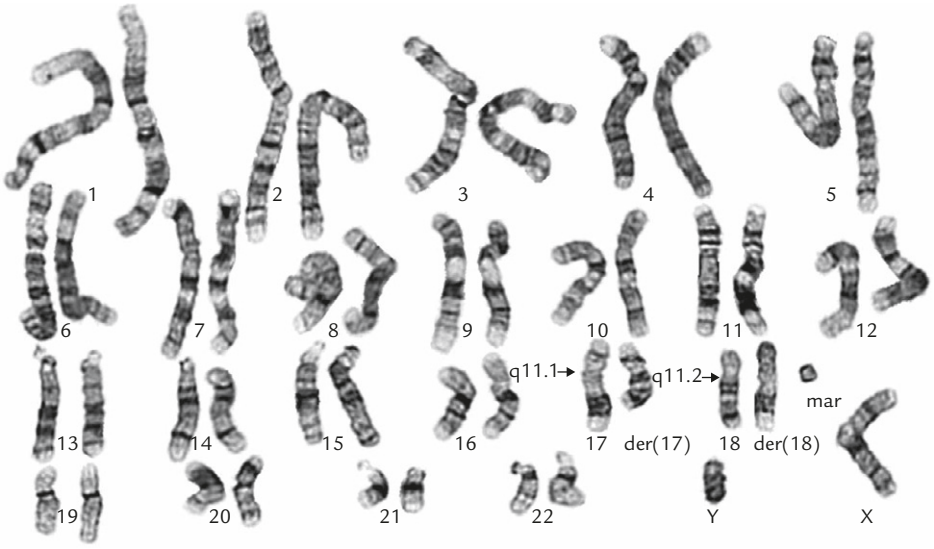

Figure 1. A 47,*XY*,t(17;18)(q11.1;q11.2),+mar karyotype. The arrows indicate the breakpoints on normal chromosomes.

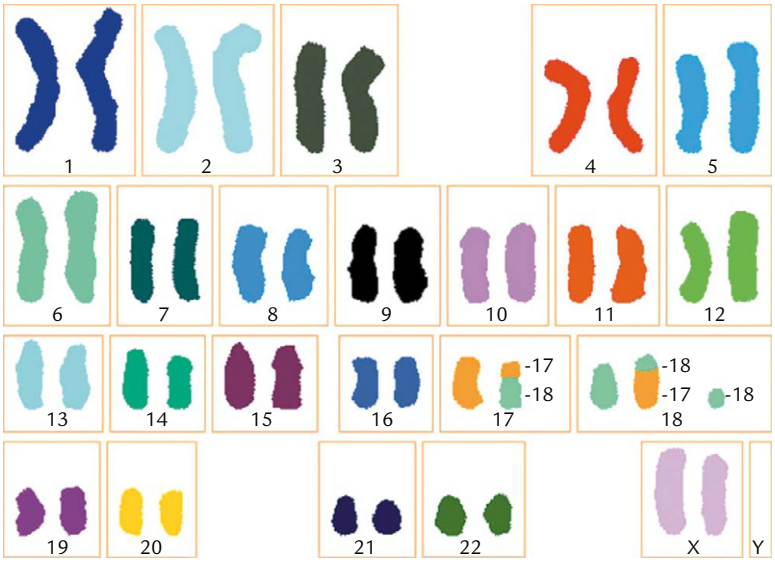

Figure 2. Spectral karyotyping using 24-color spectral karyotyping probes demonstrate a reciprocal translocation involving chromosomes 17 and 18, and a marker chromosome derived from chromosome 18.

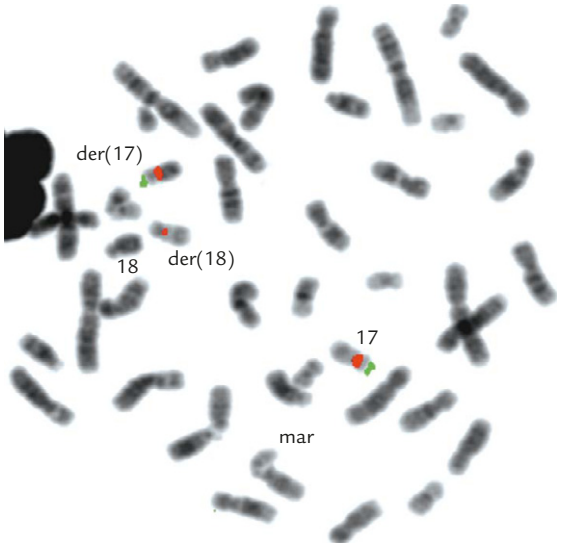

Figure 3. Fluorescence *in situ* hybridization using a 17p-specific telomeric probe (spectrum green) and chromosome 17 centromeric probe (spectrum red) shows a red signal on chromosome 17, derivative chromosome 17 [der(17)] and der(18) but not on the marker chromosome (mar).

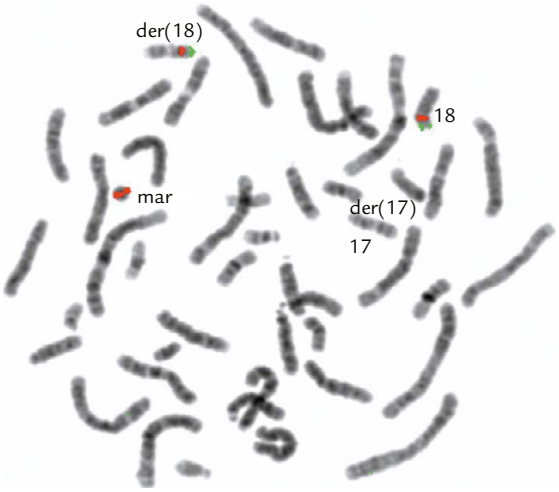

Figure 4. Fluorescence *in situ* hybridization using an 18p-specific telomeric probe (spectrum green) and chromosome 18 centromeric probe (spectrum red) shows a red signal on chromosome 18, der(18) and marker chromosome mar.

q11.2)(18pTEL+,D18Z1+,D17Z1+),+der(18)(D18Z1+). Oligonucleotide-based aCGH demonstrated no gain or loss of the gene dosage on chromosomes 17 and 18.

Discussion

To date, at least seven cases of sSMCs with minute centric fragments of chromosome 18 have been reported [10]. Starke et al [11] and Liehr et al [12] reported the prenatal diagnosis of 47,XY,+mar *de novo* in all 15 colonies of amniocytes because of advanced maternal age and fetal cystic hygroma. The sSMC was ascertained to be min(18)(:p11.1→q11.1:) with positive cep18 by cenM-FISH and subcenM-FISH, and the pregnancy was terminated. Starke et al [11] and Manvelyan et al [13] reported the diagnosis of 47,XX,+mar[23]/46,XX[17] in the peripheral blood of a 36-year-old female with primary infertility and an atrial septal defect. The sSMC was ascertained to be min(18)(:p11.21→q11.1:) with positive pcp18 and cep18 by cenM-FISH and subcenM-FISH and RP11-151D11(13.08 Mb) on the sSMC. Backx et al [14] and Tönnies et al [15] reported the diagnosis of 47,XY,+mar[21]/46,XY[2] at 6 years of age and 47,XY,+mar[25]/46,XY[9] at 18 years of age in a normal healthy adolescent male whose healthy mother

also had 26% mosaicism for marker chromosome. The sSMC was ascertained to be min(18)(:p11.21→q11.1:) by cenM-FISH and subcenM-FISH with positive RP11-151D11(13.08 Mb) and a 13.99 Mb-centromere dosage gain by aCGH. Liehr [10] reported the diagnosis of 47,*XX*,+mar[26]/46,*XX*[14] in the peripheral blood of a healthy, normal 31-year-old woman. The sSMC was ascertained to be min(18)(:p11.21→q11.1:) by cenM-FISH and subcenM-FISH with a breakpoint in 18p between RP11-794M8 (13.03 Mb) and RP11-411B10 (13.99 Mb) using bacterial artificial chromosomes (BACs). Baldwin et al [16] reported 47,*XX*,+mar (80%)/46,*XX* (20%) in an adult female who had difficulty in conceiving. The marker chromosome was also found in her normal father and normal daughter. The sSMC was ascertained to be mar(18)(:p11.21→q11.1:) by subcenM-FISH, and 1 Mb in size on sSMC using BACs and aCGH. Baldwin et al [16] additionally reported the prenatal diagnosis of 47,*XX*,+ mar (100%) *de novo* by amniocentesis because of an advanced maternal age. The additional case reported by Baldwin et al was normal with no dysmorphic features or developmental delay at 4 months of age. The sSMC was ascertained to be mar(18) (:p11.21→q11.1:) by subcenM-FISH, and 2.6 Mb in size on sSMC as determined by BACs and aCGH. Liehr et al [6] reported the diagnosis of 47,*XX*,+ mar(100%) *de novo* in the peripheral blood of a 1-month-old girl without visible clinical signs, except hyperbilirubinemia, an atrial septal defect and open ductus Botalli. The sSMC was ascertained to be min(18)(:p11.1→q11.2:) by cenM-FISH and subcenM-FISH. Our case adds to the reported cases of sSMCs derived from the centromeric region of chromosome 18 without phenotypic consequences.

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