

Short Communication

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

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Accepted 25 May 2012

## Abstract

**Objective:** To present prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome (sSMC) derived from ring chromosome 2 [r(2)].

**Methods and Results:** A 35-year-old woman underwent amniocentesis at 17 weeks of gestation, because of advanced maternal age. Amniocentesis revealed a *de novo* ring-shaped sSMC in 11 of 23 colonies of cultured amniocytes. Repeated amniocenteses were made. The sSMC was characterized by array comparative genomic hybridization (aCGH), interphase fluorescence *in situ* hybridization (FISH) and quantitative fluorescent polymerase chain reaction (QF-PCR) on uncultured amniocytes. In uncultured amniocytes, aCGH showed a 39.49-Mb genomic gain in chromosome 2 encompassing 2q11.2→q21.2, interphase FISH revealed a mosaic level of 52% (52/100 cells), and QF-PCR manifested a diallelic pattern for chromosome 2, with gene dosage increase in the paternal allele of proximal 2q-specific DNA markers. In cultured amniocytes, the sSMC was characterized by metaphase FISH, spectral karyotyping (SKY) and multicolor banding (MCB) to contain the centromere and proximal 2q, and the karyotype was 47,XX,+r(2)(p11.1q21.2)[14]/46,XX[11]. The pregnancy was terminated. The fetus postnatally manifested facial dysmorphisms. Postnatal cytogenetic analyses revealed the karyotypes of 47,XX,+r(2)[12]/46,XX[28] in cord blood, 47,XX,+r(2)[7]/46,XX[33] in umbilical cord, 47,XX,+r(2)[13]/46,XX,+idic r(2)[3]/46,XX[24] in placenta and 47,XX,+r(2)[8]/46,XX,+idic r(2)[1]/46,XX[31] in amnion.

**Conclusion:** Molecular cytogenetic techniques such as aCGH, interphase FISH and QF-PCR on uncultured amniocytes, and SKY, MCB and metaphase FISH on cultured amniocytes are useful for characterization of the nature of a prenatally detected sSMC.

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**Keywords:** duplication of 2q11.2→q21.2; prenatal diagnosis; ring chromosome 2; small supernumerary marker chromosome 2

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## Introduction

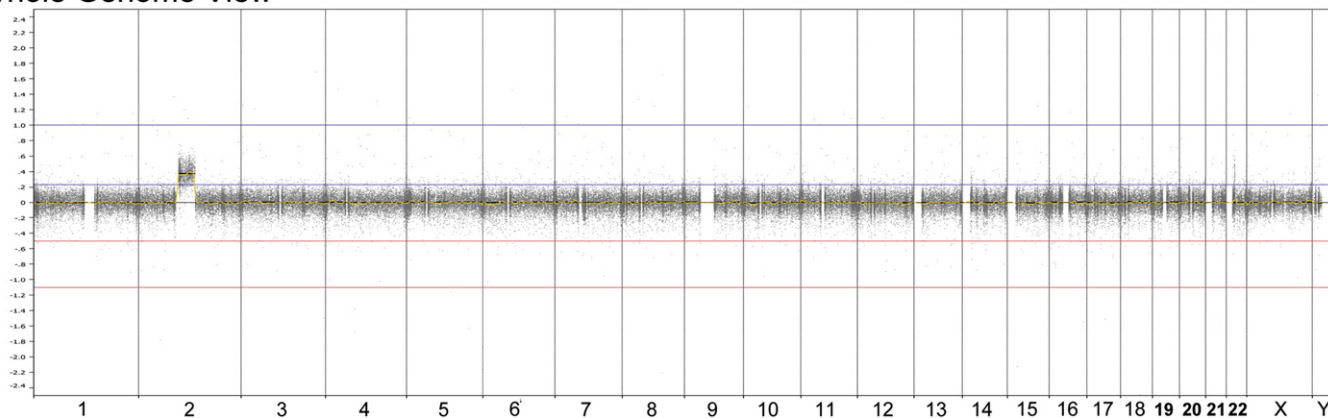
A small supernumerary marker chromosome (sSMC) is a structurally abnormal chromosome  $\leq$  the size of chromosome 20 and cannot be characterized by conventional banding techniques [1–8]. A ring chromosome arises from breakage in the short arm and the long arm of a chromosome, with subsequent fusion at the breakpoints and loss of the segments distal to the breakage. sSMCs appear in about 0.075% of prenatal cases and in about 0.044% of newborn infants [1,3,9]. Ring chromosomes occur in 0.004% of recognized conceptions and can originate from all human chromosomes [10]. About 70% of sSMCs are associated with a *de novo* event [11]. About 70% of sSMCs originate from acrocentric chromosomes [1,12]. About 70% of *de novo* sSMCs have no phenotypic effects [9]. Prenatal diagnosis of an SMC may cause difficulties in genetic counseling and requires multidisciplinary management [13]. Molecular cytogenetic techniques, such as fluorescence *in situ* hybridization (FISH), spectral karyotyping (SKY), multicolor banding (MCB), array comparative genomic hybridization (aCGH) and quantitative

fluorescent polymerase chain reaction (QF-PCR) are helpful in identification of the nature of the sSMC [4–8]. Prenatal diagnosis of a supernumerary ring chromosome 2 [r(2)] is very uncommon. Here, we present our experience of prenatal diagnosis and molecular cytogenetic characterization of mosaicism for an sSMC derived from r(2) using aCGH, interphase FISH and QF-PCR on uncultured amniocytes, and SKY, MCB and metaphase FISH on cultured amniocytes.

## Materials, methods and results

A 35-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation at a local clinic because of advanced maternal age. Her husband was 32 years old. Cytogenetic analysis of the cultured amniocytes showed mosaicism for a ring-shaped sSMC. Of 23 colonies of cultured amniocytes, 11 colonies had an sSMC, whereas the rest were normal. The karyotype was 47,XX,+r(2)[11]/46,XX[12]. aCGH on cultured amniocytes revealed no genomic imbalance. The woman was referred to a medical center at 22 weeks of gestation for confirmation, and a repeat amniocentesis was

### Whole Genome View



### Chromosome 2

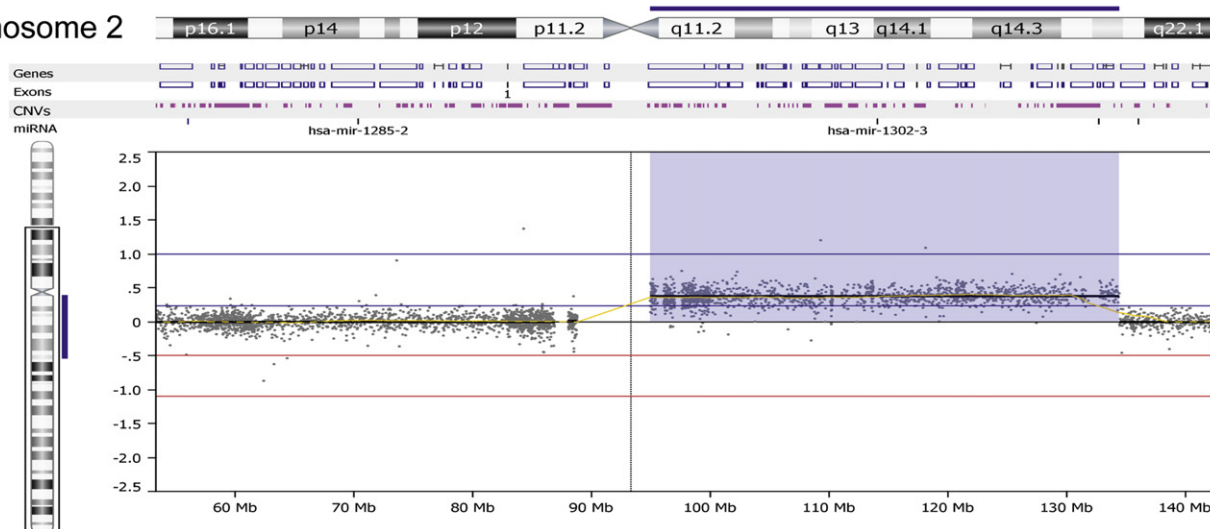


Fig. 1. Array comparative genomic hybridization (aCGH) using whole-genome NimbleGen CGX-12 array on uncultured amniocytes shows a 39.49-Mb genomic gain in chromosome 2 encompassing 2q11.2→q21.2 (94,977,959 – 134,464,973 bp).

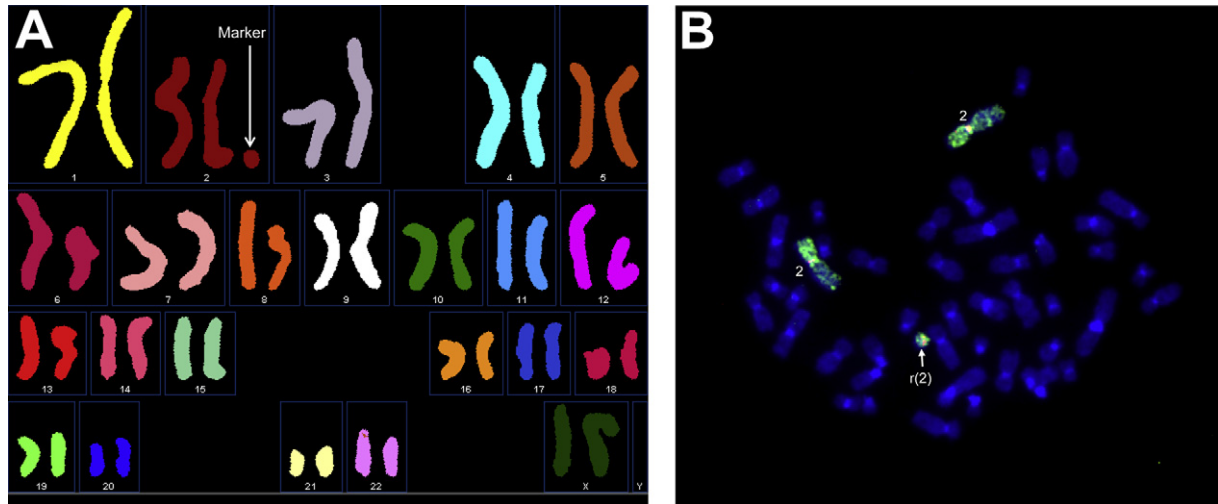


Fig. 2. (A) spectral karyotyping (SKY) using 24-color SKY probes shows a small supernumerary marker chromosome (arrow) derived from chromosome 2; (B) metaphase fluorescence *in situ* hybridization (FISH) using a chromosome 2 whole painting probe (WCP2) (spectrum green) and a chromosome 2  $\alpha$ -satellite probe (CEP2) (spectrum red) shows a chromosome 2-derived ring chromosome 2 with a chromosome 2 centromere.

performed. Molecular cytogenetic techniques were applied to the uncultured and cultured amniocytes. The aCGH investigation using whole-genome NimbleGen CGX-12 array (Roche NimbleGen, Madison, WI, USA) on uncultured amniocytes manifested a 39.49-Mb genomic gain in chromosome 2 encompassing 2q11.2→q21.2 (94,977,959–134,464,973 bp) (UCSC hg18, NCBI Build 36, March 2006) (Fig. 1). The sSMC was characterized by SKY using 24-color SKY probes (Applied Spectral Imaging, Carlsbad, CA, USA), metaphase FISH using the whole chromosome painting probe 2 (WCP2) (Cytocell, Adderbury, Oxfordshire, UK) and the chromosome 2  $\alpha$ -satellite probe (CEP2) (Cytocell), and MCB (MetaSystem, Altussheim, Germany) on cultured amniocytes. SKY and metaphase FISH analyses revealed that the sSMC originated from chromosome 2 (Fig. 2). MCB analysis showed that the sSMC was a r(2), consisting of the centromere of chromosome 2 and proximal 2q (Fig. 3). The results indicated that the sSMC was a supernumerary r(2) of r(2)(p11.1q21.2) or r(2)(::p11.1→q21.2::). The cultured amniocytes in the repeated amniocentesis showed a karyotype of 47,XX,+r(2)

(p11.1q21.2)[14]/46,XX[11] (Fig. 4). The parental karyotypes were normal. Prenatal ultrasound findings were unremarkable. At 24 weeks of gestation, an additional amniocentesis was performed for evaluation of the mosaic sSMC status on uncultured amniocytes. Molecular cytogenetic techniques, such as interphase FISH and QF-PCR, were applied to the uncultured amniocytes. Polymorphic DNA marker analysis of the uncultured amniocytes using chromosome 2-specific microsatellite markers, revealed a biparental diallelic pattern for chromosome 2, with gene dosage increase in the paternal allele of proximal 2q-specific DNA markers (Fig. 5, Table 1). Interphase FISH analysis on uncultured amniocytes using a 2q11.1-specific probe (RP11-468G5) (spectrum green) and a 2q14.3-specific probe (RP11-165G8) (spectrum red) showed three green signals and three red signals in 52% (52/100 cells) of uncultured amniocytes, and two green signals and two red signals in 48% (48/100 cells) of uncultured amniocytes (Fig. 6), indicating a high mosaic level of the sSMC in uncultured amniocytes. The microsatellite markers specific for proximal 2q, such as D2S410 (2q14.1) and D2S1328 (2q14.3),

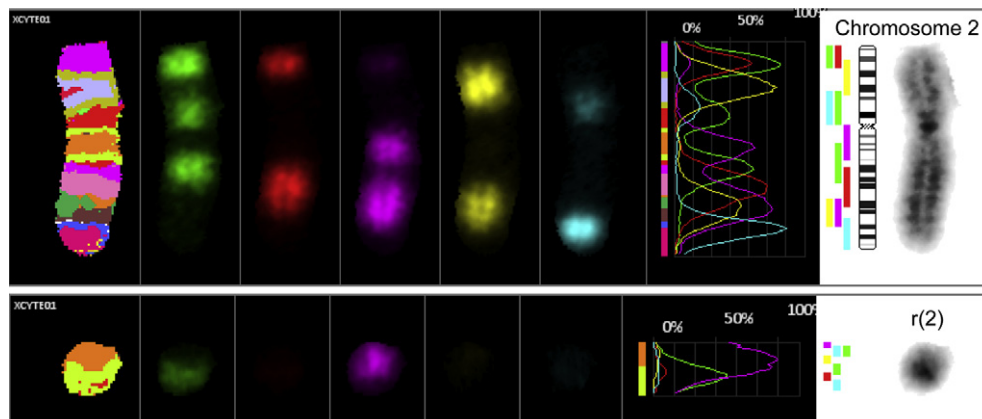


Fig. 3. Multicolor banding (MCB) analysis shows that the ring chromosome 2 contains the centromere of and proximal portion of chromosome 2.

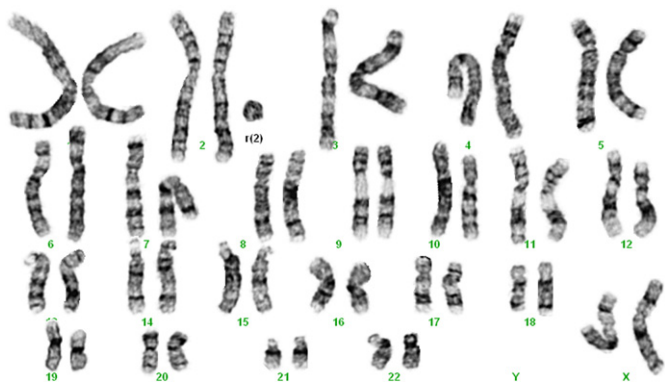


Fig. 4. A karyotype of 47,XX,+r(2). r(2): ring chromosome 2.

revealed gene dosage increase in the paternal allele, indicating a paternal origin of the sSMC. The pregnancy was subsequently terminated, and a 786 g malformed fetus was delivered with hypertelorism, epicanthic folds, depressed nasal bridge, long philtrum and low-set ears (Fig. 7). Postnatal cytogenetic analyses revealed the karyotypes of 47,XX,+r(2) [12]/46,XX[28] in cord blood, 47,XX,+r(2)[7]/46,XX[33] in umbilical cord, 47,XX,+r(2)[13]/47,XX, +idic r(2)[3]/46,XX [24] in placenta and 47,XX,+r(2)[8]/47,XX,+idic r(2)[1]/46,XX[31] in amnion (Fig. 8).

Discussion

The present case shows a difference in the ability of identification of mosaicism between different products of array chips, even under circumstances of high-grade mosaicism in amniocytes. This result is in accordance with our previous

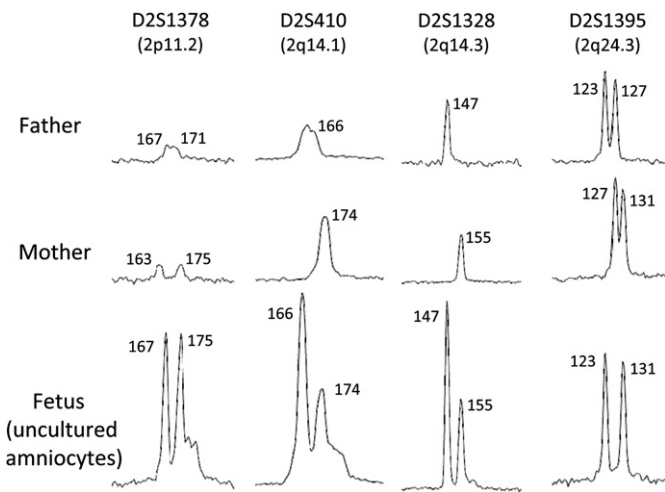


Fig. 5. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction (QF-PCR) assays at short tandem repeat markers specific for chromosome 2 on uncultured amniocytes. The markers D2S1378 (2p11.2), D2S410 (2q14.1), D2S1328 (2q14.3) and D2S1395 (2q24.3) show two different parental alleles. The marker D2S410 (2q14.1) shows two peaks (166 bp: 174 bp; paternal allele: maternal allele) and the marker D2S1328 (2q14.3) shows two peaks (147 bp: 155 bp; paternal allele: maternal allele) with a dosage increase in the paternal allele.

Table 1  
Molecular results using polymorphic DNA markers specific for chromosome 2.

Markers	Locus	Father	Mother	Fetus (uncultured amniocytes)
D2S1387	2p11.2	167, 171	163, 175	167, 175
D2S410	2q14.1	166, 166	174, 174	166 <sup>a</sup> , 174
D2S1328	2q14.3	147, 147	155, 155	147 <sup>a</sup> , 155
D2S1395	2q24.3	123, 127	127, 131	123, 131

Alleles (basepair sizes) are listed below each individual.

<sup>a</sup> With dosage increase.

observations that the detection rate of mosaicism using aCGH is variable according to different products of array chips [14–18]. The present case also shows the usefulness of interphase FISH, QF-PCR and aCGH on uncultured amniocytes for rapid confirmation of mosaicism, as well as determination of the nature of the sSMC. In this study, cultured amniocytes in two different amniocenteses revealed a mosaic level of 47.8% and 64%, respectively, uncultured amniocytes on interphase FISH revealed a mosaic level of 52%, and cultured lymphocytes revealed a mosaic level of 30%. There is a significant discrepancy of the mosaic level between amniocytes and lymphocytes, and interphase FISH on uncultured amniocytes provides valuable information on the mosaic level in amniocytes.

The present case had mosaicism for the supernumerary r(2) and a 39.49-Mb genomic gain of 2q11.2–q21.2 in association with phenotypic abnormalities. Duplications involving chromosome 2q (2q11.2→q21) have been associated with phenotypic abnormalities [19–21]. Glass et al [19] reported two familial cases of partial trisomy 2q (2q11.2→q21.1), resulting from an interchromosomal insertion of 46,XX, der(8),ins(8;2)(p21.3;q21.1q11.2) in a 37-year-old female and her 66-year-old mother, both of whom had mild mental retardation, short stature, dysmorphic features, insulin dependent diabetes mellitus and a psychotic illness. Cooke et al [20] reported a 7-year-old boy with moderate learning disability, facial dysmorphism of broad, flat and low nasal bridge, low-set ears, epicanthic folds, strabismus, clinodactyly and a *de novo* duplication of chromosome 2q (2q11.2→q21). Wang et al [21] reported a 32-gestational-week female fetus with agenesis of the corpus callosum, Dandy-Walker malformation, hydrocephalus, cleft palate, lung hypoplasia, a hypoplastic bladder, atretic ureters, absent right thumb, club foot and a triplication of chromosome 2q (2q11.2→q21).

Duplications involving 2q11.2–q14 have been associated with phenotypic abnormalities [22–24]. Mu et al [22] reported a 3.5-year-old girl with short stature, microcephaly, brachycephaly, depressed nasal bridge, prominent philtrum, congenital glaucoma, mental retardation and a *de novo* direct duplication of chromosome 2q (2q11.2→q14). Ostroverkhova et al [23] reported an 18-month-old boy with mental retardation, dolichocephaly, coarse hair, low-set ears, exophthalmos, epicanthic folds, strabismus, depressed nasal bridge, high-arched palate, excess neck skin, tapered fingers, clinodactyly, inguinal hernia, hypogenitalism, muscular hypotonia



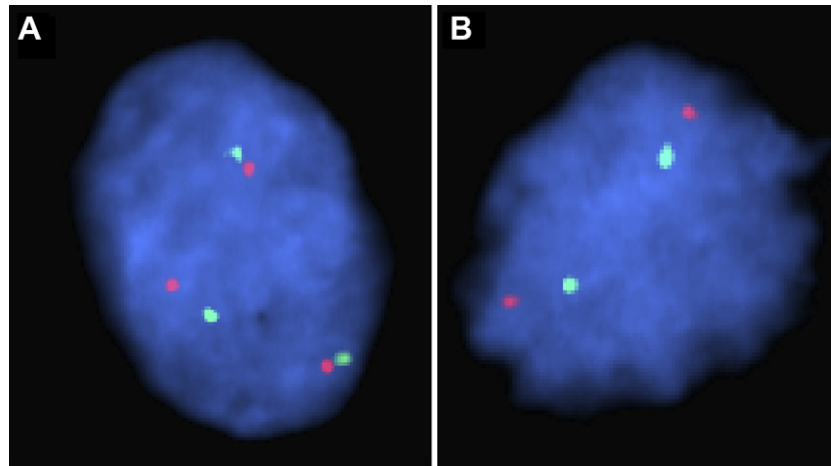


Fig. 6. Interphase FISH analysis on uncultured amniocytes using a bacterial artificial chromosome (BAC) probe RP11-468G5 (2q11.1; spectrum green) and a BAC probe RP11-165G8 (2q14.3; spectrum red) shows (A) three green signals and three red signals in an abnormal cell with a supernumerary r(2); and (B) two green signals and two red signals in a normal cell.

and 50% mosaicism for an sSMC as r(2)(p11.2→q14.1). Wang and Hunter [24] reported a 17-year-old girl with mental retardation an sSMC with dup(2)(p11→q14).

A duplication involving 2q11.2-q13 has been associated with phenotypic abnormalities. Riegel and Schinzel [25] reported a 4-year-old boy with a left cleft lip, cleft palate, microcephaly, epilepsy, mental retardation, a high frontal hairline, a short and broad nose with a prominent bridge, tapered fingers, proximally implanted big toes, hypoplasia of hallux nails, right cryptorchidism, hypoplastic scrotum and a duplication of chromosome 2 (2q11.1→q13.2).

An sSMC(2) involving 2q11.2 or 2q12 may or may not be associated with phenotypic abnormalities [26–29]. Villa et al [26] identified an sSMC as r(2)(p10q11.2) with 29% mosaicism for the r(2) in cultured amniocytes and 44% mosaicism for the r(2) in fetal lymphocytes at prenatal diagnosis due to advanced maternal age. Postnatal follow-ups confirmed a normal female baby with normal development. Giardino et al

[27] reported two familial cases of mosaic r(2)(q10q11.2) in a 6-year-old boy and his 41-year-old mother, with 80% and 54% mosaicism for the r(2), respectively. The son had mental retardation, psychotic behavior, hyperactivity, brachycephaly and minor dysmorphisms, and the mother had minor dysmorphisms. Giardino et al [28] identified an sSMC as r(2)(p11.1q12.3) with 91.9% mosaicism for the r(2) in cultured amniocytes and 40% mosaicism for the r(2) in fetal lymphocytes at prenatal diagnosis due to advanced maternal age. Postnatal autopsy revealed a normal male fetus without malformations. In a review of 18 cases with an sSMC(2) involving 2q11.2 or 2q12, Liehr [29] found that 9 cases (50%) were associated with no abnormal clinical findings, and 9 cases (50%) had abnormal clinical findings.

We have demonstrated the usefulness of molecular cytogenetic techniques on uncultured amniocytes for evaluation of a supernumerary r(2). Through the use of uncultured amniocytes, the nature of a *de novo* non-acrocentric sSMC with



Fig. 7. Craniofacial appearance of the proband at birth.

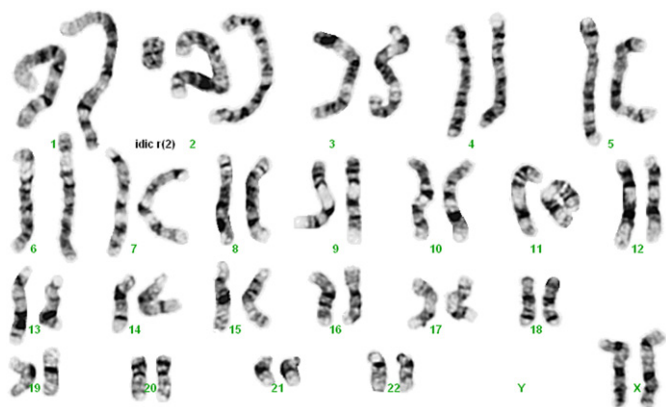


Fig. 8. A karyotype of 47,XX,+idic r(2). idic r(2): isodicentric ring chromosome 2.

high-grade mosaicism can be well characterized by aCGH, the mosaic level of the sSMC can be determined by interphase FISH, and uniparental disomy can be excluded by QF-PCR. Additional SKY, MCB and metaphase FISH on cultured amniocytes are useful for confirmation of the chromosome aberration. We conclude that molecular cytogenetic techniques, such as aCGH, interphase FISH, QF-PCR, SKY, MCB and metaphase FISH, are helpful in genetic counseling of prenatally detected sSMCs, by providing immediate and thorough information on the origin and genetic component of the sSMC.

## Acknowledgments

This work was supported by research grant NSC-99-2628-B-195-001-MY3 from the National Science Council, and MMH-E-100-04 from Mackay Memorial Hospital, Taipei, Taiwan.

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