Small Supernumerary Marker Chromosomes 1 With a Normal Phenotype

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Small supernumerary marker chromosomes (sSMCs) are a major problem in prenatal cytogenetic diagnostics. Over two-thirds of cases carrying an sSMC derived from chromosome 1 are associated with clinical abnormalities. We report 3 further cases of such sSMCs that did not show any clinical abnormalities. All 3 sSMCs studied were detected prenatally and characterized comprehensively for their genetic content by molecular cytogenetics using subcentromere-specific multicolor fluorescence *in situ* hybridization, and for a possibly associated uniparental disomy. After exclusion of additional euchromatin due to the presence of sSMCs and a uniparental disomy, parents opted for continuation of the pregnancies and healthy children were born in all 3 cases. It is important to quickly and clearly characterize prenatal sSMCs. Also, all available sSMC cases need to be collected on a homepage such as the Jena Institute of Human Genetics and Anthropology sSMC homepage (http://www.med.uni-jena.de/fish/sSMC/00START.htm). [*J Chin Med Assoc* 2010;73(4):205–207]

Key Words: chromosome 1, genotype–phenotype correlation, molecular cytogenetics, small supernumerary marker chromosomes (sSMCs), uniparental disomy

Introduction

Small supernumerary marker chromosomes (sSMCs) are reported to be a major problem, especially in prenatal cytogenetic diagnostics and counseling,[1] because they are structurally abnormal chromosomes that cannot be identified or characterized unambiguously by conventional banding cytogenetics alone, and are generally about the size of or smaller than chromosome 20 in the same metaphase spread.[2] Cases with a *de novo* sSMC, particularly those that are prenatally ascertained, are not easy to correlate with a clinical outcome.[3] It is well known that substantial numbers of sSMC lead to 4 specific syndromes: Pallister-Killian [=i(12p)], isochromosome 18p [i(18p)], cat-eye [i(22p~q)], and derivative chromosome 22 [der(22)t(11;22)] syndrome; otherwise they are derived predominantly from chromosomes 15 and 22.[2] Recently, the first step towards a genotype–phenotype correlation was reported and this is updated regularly on the Jena Institute of Human Genetics and Anthropology sSMC homepage (http://www.med.uni-jena.de/fish/sSMC/00START.htm).[3,4] Overall, the risk for an abnormal phenotype in prenatally ascertained *de novo* cases with sSMCs is considered to be ~13%;[5] these data have been refined to 7% (for sSMCs from chromosomes 13, 14, 21 or 22) and 28% (for all non-acrocentric autosomes),[6] and were recently suggested to be 30%.[7]

Seventy-four sSMCs derived from chromosome 1 have been reported.[4] In 59 cases, the clinical outcome is known, and only 16 (~27%) were not associated with clinical abnormalities. We report here 3 further sSMC(1) cases.

Case Reports

For all studies performed in the 3 patients, informed consent was obtained from their parents. In addition, sSMC studies carried out at the Institute of Human

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Case 01-O-p11.1/1-1

Prenatal diagnostics on amniotic fluid were carried out because of advanced maternal age. In sonography, no abnormalities were detectable. Cytogenetics revealed the karyotype 47,XY,+mar[50%]/46,XY[50%]. According to parental chromosomal analysis, the marker was *de novo*. Using centromere-specific multicolor fluorescence *in situ* hybridization (cenM-FISH) we found that the origin of the sSMC was chromosome 1 (Figure 1).[8] Subcentromere-specific multicolor FISH (subcenM-FISH) excluded the presence of centromere-near euchromatin.[3] Thus, a minute shaped centric marker chromosome min(1)(:p11.1 → q11:) or del(1)(:p11.1 → q11:) was characterized. The parents opted for continuation of the pregnancy and a healthy male child was born. The infant had a birth weight of 3,500g, a length of 52 cm, a head circumference of 35 cm and APGAR of 9/10/10.

Case 01-O-p11.1/3-3

Amniocentesis was performed because of advanced maternal age and repeated abortions, and the fetal karyotype 47,XX,+mar[5]/46,XX[23] was found. CenM-FISH and subcenM-FISH revealed min(1)(:p11.1→q12:) or del(1)(:p11.1→q12:) (Figure 1).[3,8] In 10% of *de novo* sSMC cases, a uniparental disomy (UPD) is observed in the sister chromosomes of the marker chromosome.[2] For chromosome 1, 2 such cases have been reported.[9,10] Thus, we performed microsatellite analysis[6] using the following markers: D1S468*, D1S1612*, D1S1597, D1S552, D1S1622, D1S3721, D1S2134, GATA165C03, D1S1665*, D1S551, D1S1588, D1S1631*, GATA176G01, D1S1679*, D1S1677, D1S1589, D1S518*, D1S1660, D1S1678, D1S2141*, D1S549, and D1S3462*. All markers with asterisks were informative normal and UPD 1 was excluded. The outcome of this pregnancy was a healthy child who was also perfectly normal at 1 year of age.

Case 01-O-p10/1-1

A chorion biopsy was carried out because of advanced maternal age and maternal mucopolysaccharidosis II with a known mutation (c708G>A). CenM-FISH and subcenM-FISH revealed the karyotype 47,XY,+min(1)(:p10→q12:)[2]/46,XY[28] (Figure 1). However, in a follow-up amniocentesis, min(1)(:p10→q12:) and del(1)(:p10→q12:) were not found again in 100 analyzed metaphases. After exclusion of UPD 1 (informative markers: D1S1597, D1S552, D1S3721, GATA165C03, GATA176G01, D1S534, D1S1679, D1S1660, D1S2141, D1S549, D1S547) and a parental origin of the marker, the parents decided to continue the pregnancy and a healthy child was born.

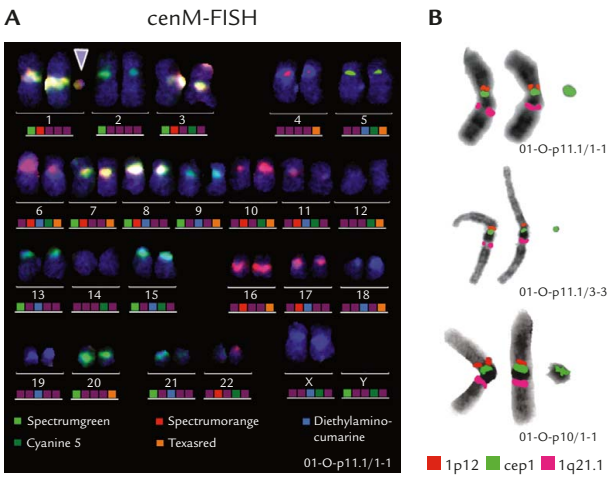

Figure 1. (A) Centromere-specific multicolor fluorescence *in situ* hybridization showed in all 3 cases the origin of the small supernumerary marker chromosomes from chromosome 1. Case 01-O-p11.1/1-1 is shown as a representative example. The small supernumerary marker chromosome is marked by an arrowhead, and the labeling used for each of the centromeric regions is depicted below each chromosome. (B) Subcentromere-specific multicolor fluorescence *in situ* hybridization results of all 3 studied cases are shown. The bacterial artificial chromosome probes RP11-130B18 in 1p12 and RP11-A35B4 in 1q21.1 were applied, as well as the alpha satellite probe D1/5/19Z1 (cep 1) and partial chromosome paints for the long and the short arms of chromosome 1. Data for the partial chromosome paints are not shown.

Since children were postnatally clinically normal, none of the parents agreed to another cytogenetic analysis from peripheral blood to confirm the results of prenatal chromosomal analysis.

Discussion

We have detected 3 new, prenatal cases with an sSMC derived from chromosome 1. All of the cases were comprehensively studied and shown to contain no euchromatic material. In addition, a UPD of sSMC sister chromosomes was excluded. It has been shown previously that a UPD can develop in sSMCs due to trisomic rescue and can lead to clinical imprinting syndromes or the activation of recessive mutated genes by iso-UPD.[2,3] All of our results were obtained within 1–2 weeks and this enabled the parents to make an informed decision with regards to continuation of the pregnancy. Since all 3 sSMCs reported did not contain

detectable euchromatin, the genotype–phenotype correlation was conclusive.[3,4] Moreover, in case 01-O-p10/1-1, a cultural artifact in the chorionic cell preparation could not be excluded. It would have been more complicated if euchromatin was present, as cases with and without clinical signs are reported for partial trisomies of 1p11.2 and 1q21.1. Only further array-comparative genomic hybridization (aCGH) and/or single copy FISH-based studies can help to determine euchromatin presence.[11,12] However, in the present 3 cases, aCGH would have led to non-informative results, because the sSMC contained no euchromatic material. According to our experience in ~80 cases studied by aCGH, this procedure is never, in isolation, fully informative in sSMC cases. Because of mosaic problems, partial trisomies cannot usually be clearly distinguished from partial tetrasomies. If only small euchromatic parts are on an sSMC, it is difficult to find that imbalance without previous knowledge of sSMC origin, and in heterochromatic sSMCs derived from acrocentric chromosomes, false-positive results can be obtained especially for the pericentric regions of chromosome 9. In addition, cryptic sSMC mosaics[3] are missed when aCGH is used in isolation.

In conclusion, a central collection of all sSMC cases, such as that on the Jena Institute of Human Genetics and Anthropology sSMC homepage, would be desirable. On this website, there are similar sSMC cases with identical clinical outcomes, but there are also occasional exceptions with variant outcomes that can be due to: (1) an sSMC that does not cause disease may be associated with a UPD of the sSMC sister chromosomes; (2) an sSMC that is not related to the clinical abnormalities reported in a patient, but where the real disease-causing mutation is not found; or (3) an sSMC which is not well-characterized and where seemingly similar sSMCs are, in reality, a different size.

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