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CASE REPORT

# Small Supernumerary Marker Chromosome Derived from Proximal p-Arm of Chromosome 2: Identification by Fluorescent *in Situ* Hybridization

Ružica Lasan Trčić, Vlasta Hitrec, Ljiljana Letica, Mario Ćuk, Davor Begović

*Division of Genetics and Metabolism, Cytogenetic Laboratory, Department of Pediatrics, Zagreb University Hospital Center, Zagreb, Croatia*

Conventional cytogenetics detected an interstitial deletion of proximal region of p-arm of chromosome 2 in a 6-month-old boy with a phenotype slightly resembling Down's syndrome. The deletion was inherited from the father, whose karyotype revealed a small ring-shaped marker chromosome, in addition to interstitial deletion. Fluorescence in situ hybridization identified the marker, which consisted of the proximal region of the p-arm of chromosome 2, including a part of its centromere. This case shows that molecular cytogenetic analysis can reveal the mechanism of the formation of the marker chromosome.

***Key words:*** *chromosome aberrations; chromosomes, human, pair 2; genetic markers; in situ hybridization, fluorescent; karyotyping; ring chromosomes*

Supernumerary marker chromosomes are small chromosomes, which usually lack a distinct banding pattern and are therefore rarely identifiable by conventional banding cytogenetics alone (1). They are relatively rare in general population (0.24/1,000 live births) but are more frequent (3.27/1,000) in mentally subnormal population (2). This heterogeneous group of chromosomes comprises a mixed collection of structurally rearranged, mainly pericentromeric chromosome regions, but the clinical consequences of thus rearranged chromosome regions remain unclear (3,4). Supernumerary ring chromosomes account for about 10% of supernumerary marker chromosomes (5). Molecular cytogenetic methods, such as fluorescent in situ hybridization (FISH), are highly suitable for the identification and characterization of marker chromosomes (6).

We present a case of supernumerary marker chromosome derived from the chromosome 2. It was identified by FISH in the phenotypically normal father of a 6-month-old dysmorphic boy referred to cytogenetic investigation because of the slight resemblance to the Down syndrome.

## Case Report

Using conventional banding cytogenetics on the lymphocyte culture, we detected an interstitial deletion of chromosome 2 [del (2)(p11.1p12)] in the 6-month-old boy, the first child of young and healthy parents. The first examination revealed well-developed infant with some dysmorphic features consisting of a prominent forehead; mongoloid palpebral fissures; epicanthic folds; broad nasal bridge; short, well-formed philtrum; low-set protruding ears; and bilateral simian crease. All laboratory findings were normal. On further examinations, he showed signs of mild psychomotoric developmental delay. At the age of two, his speech was poorly developed for that age.

Karyotyping of the parents revealed that the father carried small, ring-shaped, supernumerary marker chromosomes, in addition to the interstitial deletion (Fig. 1). Marker chromosome identification with FISH was performed by using all human centromere probes (Oncor Inc, Gaithersburg, MD, USA) on chromosome spreads obtained from peripheral blood cells. Three positive signals were revealed by a specific-probe from the chromosome 2. The proximal break, passing through the centromere 2, split the chromosome 2-specific alpha satellite centromeric fragments into two smaller units creating the functional centromere of the marker chromosome (Fig. 2). The whole chromosome paint (wcp) probe (Cytocell, Banbury, UK) for the chromosome 2 specifically hybridized to marker chromosome, whereas no signals were detected from other telomeres (data not shown) (Dako, Glostrup, Denmark). Thus, the FISH study allowed the marker chromosome to be defined as a ring chromosome derived from the chromosome 2, containing a small euchromatic region. Cytogenetic analysis was extended to the child's grandparents, who had normal karyotypes.

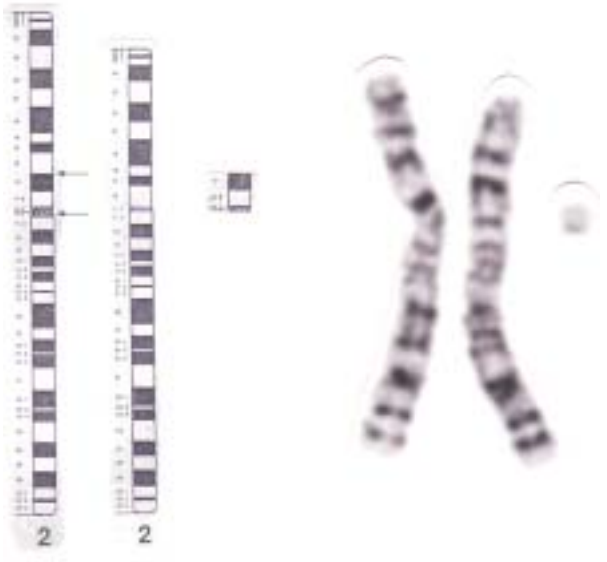


**Figure 1.** Ideogram and picture of partial metaphase (GTG-banded) of the father's chromosome 2. Arrows indicate break points.

**Figure 2.** Fluorescent in situ hybridization (FISH) of the metaphase chromosomes of the father. Note three bright signals, one on the centromere of the marker chromosome, and two on the homologue pair of chromosomes 2.

To make more accurate estimation of the extent of the ring, further FISH tests were performed with two 2p-specific YACs, 2p11.2 (747C10) and 2p13 (929A1) (Rocchi, Bari, Italy). The results confirmed the accurate break points of the deletion; the ring chromosome did not include a 2p13 band.

According to An International System for Human Cytogenetic Nomenclature (ISCN) from 1995 (1), the final karyotype was described as 47,XY,del(2)(p11.1p12),+ mar de novo. ish der (2)(wcp2+,D2Z1+).

## Discussion

Marker chromosomes are structurally abnormal chromosomes in which no part can be identified (1). This heterogeneous group of structural anomalies with different phenotypical expression, which depends on the size, genetic content, and the level of the mosaicism has been the main issue in human molecular cytogenetic investigation (7). A variety of FISH approaches have been developed, covering the entire human genome in multiple ways (8). Most supernumerary marker chromosomes have been studied by using centromere-specific DNA probes, which enabled the identification of chromosome origin (8,9), and establishment of human chromosome-specific libraries, which provided a better insight into the structural composition and genetic content of supernumerary marker chromosomes (10).

Structural deletions of the short arm of the chromosome 2 are rare (11). Developmental delay and mental retardation are present in all cases, but none of the dysmorphic features or malformations is pathognomonic for the deletion of the proximal part of 2p. Two previous cases were excluded from comparison with our proband as both had abnormalities of other chromosomes in addition to the chromosome 2 (12,13). Two other cases had deletions comprised a part of long arm of chromosome 2 (14,15). Two other published cases described patients with holoprosencephaly in relation to the deletion on the proximal part of 2p (16,17).

Only the case described by Prasher et al (11) had mental and growth retardation, together with the deletion of the band 2p13. This case shared some dysmorphic features with our case, such as a prominence of the forehead, an abnormal nasal bridge, and abnormally low-set ears and hands.

Chromosome 2 is not often involved in the formation of marker chromosome (18,19). To the best of our knowledge, there have been only five published reports in the literature concerning supernumerary ring chromosomes 2 (4,19-22) but they could not be used for the comparison with our case because their phenotypes associated with involved chromosomal material were caused by partial trysomies. The case presented in this study is a new case of supernumerary ring chromosome 2 identified by FISH, which consisted of the proximal region of p-arm of chromosome 2 including a part of the centromere 2.

There are many supernumerary ring marker chromosomes that consist of the proximal part of p- or q-arms of different chromosomes, but our case, to the best of our knowledge, is the first where molecular cytogenetic investigation illustrated the mechanism of the marker creation. This rare example shows that our marker chromosome is a part of a balanced karyotype. However, the father in our case may produce unbalanced offspring and prenatal diagnosis must be recommended.

This observation corroborates the usefulness of molecular cytogenetics in increasing the quality and accuracy of characterization and delineation of structural anomalies not resolved by conventional cytogenetics.

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**Correspodence to:**
Ružica Lasan Trčić
Division of Genetics and Metabolism
Department of Pediatrics
Zagreb University Hospital Center
Kišpatićeva 12
10000 Zagreb, Croatia
*lasan_ruzica@hotmail.com*