

## 46,XX,r(13)/46,XX, iso psu dic(13)? MOSAICISM

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### ABSTRACT

The authors report a rare case of chromosome mosaicism 46,XX,r(13)/46,XX, iso psu dic(13)? in a patient with clinical signs similar to those observed in the ring 13 syndrome (2nd category of Niebuhr (Niebuhr, R. (1977). Partial trisomies and deletions of chromosome 13. In: *New Chromosome Syndromes* (Yunis, J.J., ed.). Academic Press, New York, pp. 273-299. A hypothesis that could account for a common origin of the two cell lines is presented and the clinical and cytogenetic findings are compared to those reported in the literature.

### INTRODUCTION

The ring 13 chromosome syndrome, although rare, has been fully characterized in terms of clinical signs and symptoms, which include mental retardation, microcephaly and craniofacial dysmorphism (Parcheta *et al.*, 1985). Two categories of the disorder have been identified by Niebuhr (1977): one involving more distal chromosome breakpoints in the long arm of chromosome 13, in which the thumbs are normal, and the other with extensive chromosomal losses in which the thumbs are absent or abnormal.

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The association of a ring and of an isopseudodicentric of chromosome 13 has been described by Hutchinson-Cole *et al.* (1986), Davis and Cole (1984) and Oka *et al.* (1977). The three patients analyzed by these authors exhibited a combined phenotype of trisomy and deletion of chromosome 13, a classical trisomy of chromosome 13, and a combination of deletion and trisomy, respectively.

The present case involves a girl with r(13)/iso psu dic(13)? mosaicism and predominance of the clinical signs of the ring 13 chromosome syndrome (2nd category of Niebuhr, 1977), characterized by absent or abnormal thumbs and deletions in the 13q32 band. The possible cytogenetic mechanism for a common origin of the two cell lines, proposed by Madan *et al.* (1981), is discussed, as are the clinical differences observed between the present proposita and the cases reported in the literature.

### CASE REPORT

A.C.C., a white girl born on March 20, 1983, was the fifth child of a nonconsanguineous couple. The mother was 29 and the father 31 at the time of her birth. There were no reports of familial mental retardation and/or congenital malformations. The mother had vaginal bleeding during the third month of pregnancy and used antiabortive medication. The fetal movements started during the fifth month, were of low intensity and differed from those experienced in other pregnancies. The proposita was born at term by caesarian delivery, weighing 2,700 g. She had two episodes of pneumonia during the first year of life and was submitted to surgical correction of a rectovaginal fistula at the age of eleven months. Neuromotor development was retarded, with the child holding up her head unaided at 5 months, sitting up at 11 months and standing up with support at 5 years. Hearing loss was noted at 4 years and the child started to use a hearing aid. Physical examination, performed at 23 months, revealed: weight, 8,300 g (below the third percentile); height, 75 cm (below the third percentile); head circumference, 38.5 cm (below the second percentile); inner intercanthal distance, 28 mm (above the 97th percentile), and outer intercanthal distance, 72 mm (within the 97th percentile). It also revealed frontal bossing and low-implanted hair, both anteriorly and posteriorly and the presence of a flat, triangular hemangioma in the frontal region, sparse eyebrows, bilateral epicanthus, convergent strabismus, microphthalmia on the left and telecanthus, prominent nasal bridge, short philtrum, permanently open mouth, high-arched palate, low-implanted ears with hypoplastic helix and preauricular tag on the left. Short neck with normal movements, symmetrical chest, extrasystole upon heart auscultation, diastases of abdominal recti, female external genitalia, and anterior implantation of the anus. The upper limbs presented absence of the thumb on the right, hypoplastic thumb on the

left and bilateral short fifth fingers. The lower limbs exhibited short toes and partial syndactyly between the second and third toes (Figure 1). Neurological examination revealed apathetic behavior, overall muscle hypotonia, hyporeflexia and utterance of uncharacteristic sounds. Ophthalmological examination showed hypermetropia on the right and microphthalmia on the left. Eye fundus: pale papillae and scars in the macular and premacular region on the left. Otorhinolaryngological examination: stenotic and irregular outer auditory meatuses. Craniogram: Module = 13.0 (N = 13.0 - 16.0 - Mean = 14.8) - Index = 96 (N = 73.7 - 87.9 - Mean = 81.5). Hand X-rays; absence of the first finger on the right and hypoplastic first finger on the left. Thoracolumbar column: spina bifida at L5-S1 and sinistroconvex lumbar scoliosis. The patient had bilateral flat clubfoot with foot abduction on the right. Bone age: one year and six months (chronological age of 5 years).



Figure 1 - The proposita, aged 1 year and 11 months. Details of the skull, face, hands and feet.

## RESULTS

A total of 100 cells was examined from two 72-hour lymphocyte cultures. In all cells, one chromosome 13 was abnormal. Twenty-six percent of the cells presented

five chromosomes in the D group and one ring. In 74% of the cells, the D group consisted of five normal chromosomes and a large metacentric similar in size and morphology to one of the chromosomes in pair 3. G banding revealed that the ring was originated from a chromosome 13 which had suffered two terminal deletions in the short and long arms (13p11 and 13q32). C banding showed that the ring had two centric regions (Figure 2B). No variations in ring size or metaphases with monosomy of chromosome 13 or with two normal chromosomes 13 were observed. Analysis of the metacentric chromosome by G banding revealed that it consisted of two long arms of chromosome 13 (Figure 2A). No C banding was obtained for this chromosome and no satellite associations with the ring or with the isopseudodicentric chromosomes were observed.

Figure 3 shows the model proposed by Madan *et al.* (1981) for the formation of the two cell lines (ring/iso psu dic). The ring chromosome results from two

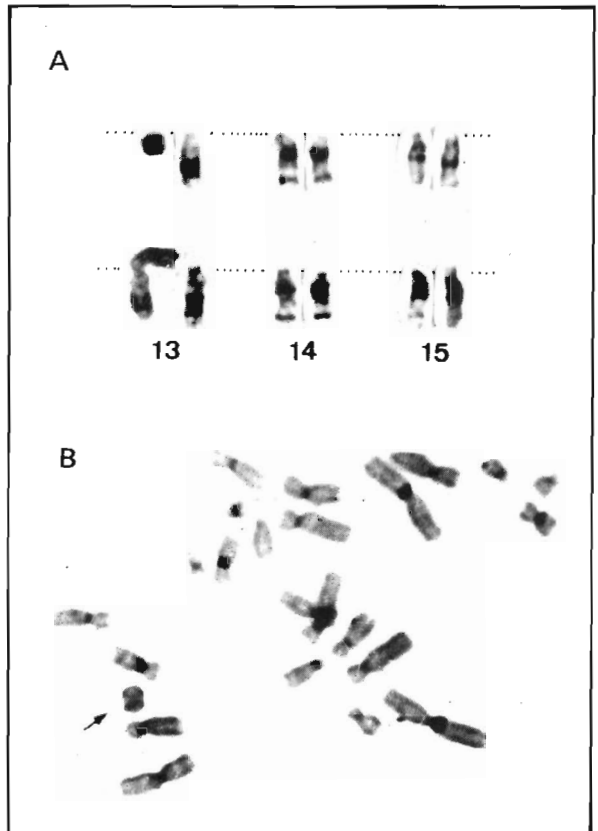
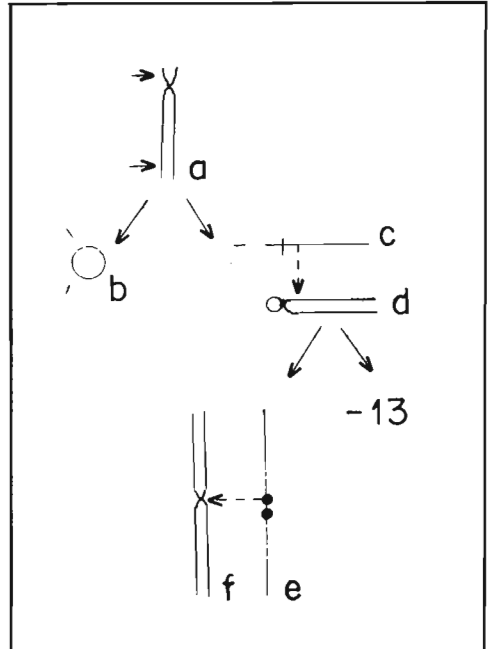


Figure 2 - (A) Group D showing the ring and iso psu dic 13 chromosome by G banding. (B) Ring chromosome 13 by C banding. The ring presents two centromeric bands.

breakpoints in one of the chromatids of chromosome 13 (p11,q32) and the isopseudodicentric from only one breakpoint in the short arm (p11) of the sister chromatid, with later duplication, fusion and inactivation in one of the centromeres (iso psu dic(13) (qter - cen - p11::p11 - cen - qter).

The karyotype of the propoita's mother was normal and the karyotype of the father could not be obtained.

Figure 3 - Common origin of a ring-13 and isopseudodicentric-13 proposed by Madan *et al.* (1981). One of the chromatids of chromosome 13 presents breaks in the long and short arms forming the ring (Figure 3B). The acentric fragments are lost or are eliminated in the subsequent division. The second chromatid exhibits a break in the short arm only, is duplicated in phase S and joins the sister chromatid through the breakpoint of the short arm (Figure 3D). At anaphase, when chromatid separation occurs, a dicentric chromatid arises which is included in the nucleus of one of the daughter cells. The other nucleus is monosomic for chromosome 13. One of the two centromeres of the dicentric chromatid undergoes deletion or inactivation, with the appearance of a stable chromosome with only one functional centromere.



### Clinical study

Table I presents the frequencies and percentages of the major clinical signs observed in 10 patients with the ring 13 chromosome syndrome reported in the literature and compared with the present case. All of these signs were present in the propoita, who also exhibited deafness, microphthalmia and retinal dysplasia, alterations that are more commonly observed in chromosome 13 trisomy (Smith, 1985).

Table I - Clinical features in patients with chromosome 13 ring syndrome.

Clinical features	A	B	C	D	E	F	G	H	I	J	Frequency	%	This Report
Mental retardation	+	+	+	+	+	+	+	+	+	+	10/10	100%	+
Microcephaly	+	+	+	+	+	+	+	+	+	+	10/10	100%	+
Inner epicanthal folds	+	+	.	+	+	+	+	.	+	+	8/10	80%	+
Broad prominent nasal bridge	+	+	+	+	+	+	.	+	+	+	9/10	90%	+
High-arched palate	.	+	.	+	+	.	.	+	.	+	5/10	50%	+
Hypertelorism	+	+	.	+	.	.	.	+	.	+	5/10	50%	+
Ear abnormality	+	+	+	+	+	.	.	+	+	+	8/10	80%	+
Genital malformation	+	+	.	+	.	.	.	+	.	+	5/10	50%	+
Absent thumb or thumbs abnormality	+	+	.	.	.	.	+	+	.	+	5/10	50%	+
Short fifth finger	.	.	+	+	.	+	.	.	.	.	3/10	30%	+
Skeletal malformation	+	+	.	+	.	.	.	+	+	.	5/10	50%	+

A: Niebuhr (1973); B: Niebuhr and Ottosen (1973); C: Zink *et al.* (1973); D: Fryns *et al.* (1974); E: Hoo *et al.* (1974b); F: Fried *et al.* (1975); G: Zdansky *et al.* (1975); H: Magenis *et al.* (1976); I: Noel *et al.* (1976); J: Lagergren *et al.* (1980).

## DISCUSSION

The phenotypic alterations observed in the proposita were similar to those described for the ring 13 syndrome (2nd category of Niebuhr, 1977) (Table I), characterized by absent or abnormal thumbs associated with other congenital malformations. However, the cytogenetic analysis revealed the presence of mosaicism which consisted of a ring resulting from 13p11 and 13q32 deletions and present in 26% of all metaphases, and of a metacentric chromosome probably of the isopseudodentric type with duplication of the long arm and present in 74% of the cells (Figures 2A and 3). The clinical similarities between the present case and Patau syndrome (13 trisomy) were limited to the following alterations: deafness, microcephaly and retinal dysplasia. All of the remaining malformations (Table I) were characteristic of the 13 ring syndrome, thus resulting mainly from deletions and in particular of the long arm of chromosome 13 (Hoo *et al.*, 1974).

Davis and Cole (1984) (apud Holland-Saumur *et al.*, 1987) reported a case of chromosome mosaicism similar to that described here. The patient had 32% of cells with r(13) and 68% with a large metacentric chromosome of the isopseudodentric type with the model of formation proposed by Madan *et al.* (1981) (Figure 3). The clinical findings were similar to those observed in classic trisomy 13 and characterized by cleft lip and palate and elevated levels of fetal hemoglobin. A second case of r(13)/rob(13q;13q) mosaicism was published by Oka *et al.* (1977), who described a patient with a combined phenotype of 13 deletion and trisomy. Hutchinson-Cole *et al.* (1986) also investigated a patient with chromosome mosaicism and a clinical picture of deletion and trisomy. The two cell lines consisted of a ring and of an acrocentric chromosome resulting from a deletion on the long arm, with later duplication and with deletion and trisomy of some segments, thus differing from the isopseudodentric chromosome described here.

Thus, the cases reported by Davis and Cole (1984) and by Oka *et al.* (1977) presented a chromosomal mosaicism similar to that described in the present study. However, the clinical alterations observed in the present proposita differ from those reported by these authors. The patient described by Davis and Cole (1984) presented the classical malformations of the 13 trisomy syndrome (Patau syndrome), and that reported by Oka *et al.* (1977) had a combined phenotype of trisomy and deletion. A preferential deletion phenotype was observed in our patient, who presented abnormal thumbs associated with other malformations (Table I) and a chromosomal breakpoint calculated to be 13q32 (Niebuhr, 1977). These clinical differences may be justified by the frequency of r(13)/iso psu dic (13) in the different tissues and organs. Although the frequencies obtained in the analysis of peripheral blood from our patient and from the patients reported by Davis and Cole (1984) and by Oka *et al.* (1977) were always

higher for the trisomic line (76% and 26%; 68% and 32%, and 75% and 25%, respectively), different concentrations of these cells may be observed in the remaining tissues, consequently leading to different clinical manifestations. Another hypothesis is related to the breakpoint in the long arm of chromosome 13 for the formation of the ring. The more extensive the deletion of this chromosome segment, the more exuberant may be the clinical manifestations, which would be superimposed to the phenotype of trisomy.

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### RESUMO

Os autores descrevem um caso raro de mosaicismo cromossômico 46,XX,r(13)/46,XX, iso psu dic (13)? em uma paciente que apresentava sinais clínicos semelhantes aos observados na síndrome do anel do cromossomo 13 (categoria 2a de Niebuhr, 1977). Discutem a hipótese de uma origem comum para as duas linhagens celulares e comparam os achados clínicos e citogenéticos aos descritos na literatura.

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