

Electronic letter

A case of ring chromosome 2 with growth retardation, mild dysmorphism, and microdeletion of 2p detected using FISH

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EDITOR—Ring chromosomes 2 are rare. We are aware of nine previously reported cases.¹⁻⁷ We report the clinical and cytogenetic aspects of a further case of ring 2 in a newborn female with severe intrauterine growth retardation (IUGR), microcephaly, heart malformation, and minor dysmorphic features.

Case report

The subject was born to a 22 year old mother and 30 year old father with no relevant medical history. The mother had two previous miscarriages at 10 and 12 weeks. Her antenatal ultrasound scans in this pregnancy were noted to be abnormal (ventriculomegaly, a two vessel cord, and IUGR). At 34 weeks a repeat ultrasound scan showed reduced liquor volume with no fetal breathing movements. An amniocyte culture was attempted but was unsuccessful. The patient was born by lower segment caesarean section at 35 weeks' gestation. Her birth weight was 1469 g and her head circumference was 29 cm (both below the 3rd centile). She was noted to be dysmorphic and showed severe IUGR. She required ventilation for respiratory distress syndrome.

The dysmorphic features include microcephaly, hypertelorism, a wide, flat nasal bridge, bilateral epicanthic folds, narrow and upward slanting palpebral fissures, arched eyebrows, a long philtrum with a thin upper lip, a short neck, right hemihypertrophy, and positional talipes (fig 1). Audiological and ophthalmological assessments have been normal to date.

In addition, she has nine café au lait patches on her skin, a bifid thumb on her left hand, and a high pitched cry. She had multiple muscular ventriculoseptal defects, which were treated conservatively, and at her most recent review had nearly closed.

On follow up until 10 months of age, she has been grossly growth retarded despite an adequate nutrition. Her weight and length are well below the 3rd centile and her head circumference is 4 SD below the mean. She remains developmentally delayed, at present able to sit supported, roll from back to front, place objects in her mouth, and babble, consistent with a developmental age of 5 months.



Figure 1 Clinical photograph of the patient.

CYTOGENETIC STUDIES

Cytogenetic analysis of cultured peripheral blood lymphocytes showed a female karyotype with a ring 2 chromosome. The ring 2 appeared to be complete; bands p24 and q36 were clearly visible in conventional G banded preparations (fig 2A). The patient's karyotype was therefore determined as 46,XX,r(2)(p25q37). A total of 100 G banded metaphases were examined. Of these, 79 cells contained the ring 2, four cells had 45 chromosomes and no ring, and one cell had 47 chromosomes with two ring 2 chromosomes. The remaining 16 cells showed various rearrangements of the ring, including missing or extra bands and rod shaped derivatives. No normal cells were seen. Both parental karyotypes were normal.

Fluorescence in situ hybridisation (FISH) studies using probes specific for the subtelomeric region of the long arm of chromosome 2 (210E15 and CEBII)⁸ showed no deletion of this region in the ring 2 (fig 2B). No deletion of

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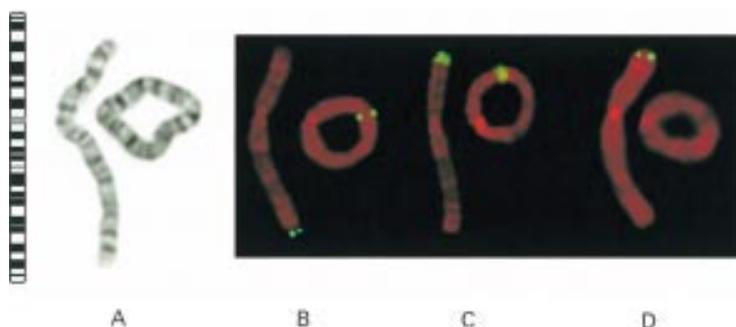


Figure 2 (A) G banded partial karyotype showing the normal chromosome 2 and ring chromosome 2. (B) Fluorescence in situ hybridisation of subtelomeric probe 210E15 to the q arms of chromosome 2 and ring chromosome 2. (C) Fluorescence in situ hybridisation with partial chromosome paint 2 (SPBP2 Biovation probe) to the p arms of chromosome 2 and ring chromosome 2. (D) Fluorescence in situ hybridisation of subtelomeric probe VIJ2yRM2052 to chromosome 2 and ring chromosome 2, showing deletion of the p arm telomeric region in the ring chromosome 2.

2p was evident using the chromosome 2 telomeric region painting probe (SPBP2 Biovation probe, fig 2C). However, additional FISH studies were carried out using the Vysis TelVysion subtelomeric probe for the short arm of chromosome 2 (VIJ2 yRM2052), which contains a locus estimated to be within 300 kb of the end of the chromosome.⁸ No signal was detected on the ring 2 with this probe (fig 2D). This is consistent with the presence of a small terminal deletion of the short arm including the region detected by the subtelomeric probe VIJ2 yRM2052.

Discussion

The striking features of the reported cases of ring 2 are IUGR, microcephaly, and postnatal growth failure. Developmental delay is also recorded in all but one of these patients. These are the main features of the “ring syndrome”, and are seen in patients with rings of other chromosomes.

The term “ring syndrome” was first applied by Côté *et al*¹ to describe those cases with an apparently entire ring chromosome associated, independently of the chromosome involved, with severe growth failure and only minor dysmorphic features. Hoo *et al*⁶ and Sutherland and Carter¹ both postulated that malformations seen in patients with a ring 13 and ring 2, respectively, were the result of the behaviour of the ring chromosome causing disturbances in the regulation of cell division, rather than as a result of genetic deletion. Côté *et al*¹ further suggested that rings which appear complete might occur by a process of telomere-telomere fusion with no loss of genetic material, the phenotypic effect being because of ring instability, during cell division, causing a high cellular death rate and consequent growth retardation. Surviving aneuploid cells may also contribute unfavourably to the phenotype. Other products of mitotic instability, such as the rod shaped derivatives of the ring 2 seen in our patient, may compound the chromosomal imbalance. Kosztolányi¹⁰ showed decreased cell viability *in vitro* in cells from patients with ring chromosomes, and in his review of 207 cases of ring chromosome¹¹ he suggests that the effect of ring instability is more pronounced in patients with rings of larger chromosomes. Gardner and Sutherland¹² presume that this is because of the increased opportunity for sister chromatid exchanges to occur, generating greater numbers of aneuploid cells, which may not be viable. Limb asymmetry, a feature seen in cases of chromosomal mosaicism, is also present in our patient. It would be reasonable to speculate that this could be because of the effect on growth rate of chromosomally unbalanced cells produced as a result of ring instability at cell division.

Table 1 Clinical features of patients with ring chromosome 2 or deletion of 2p

	Sutherland and Carter ¹	Maraschio <i>et al</i> ²	Maraschio <i>et al</i> ²	Maraschio <i>et al</i> ²	Vigfusson <i>et al</i> ³	Côté <i>et al</i> ¹	Jansen <i>et al</i> ⁵	Wyandt <i>et al</i> ⁶	Lacassie <i>et al</i> ⁷	Present report	Francis <i>et al</i> ¹⁵
Estimated breakpoints	p25q37	p25q37	p25q37 t(2/6)	?	p25q37	p25q37	p25q37	p25.2q33.2	p25q37.3	p25q37	del(2)(p24)
IUGR	+	+	+	+	+	+	+	-	+	+	-
Postnatal growth retardation	+	+	+	+	+	+	+	+	+	+	+
Microcephaly	+	+	+	+	+	+	+	+	+	+	+
Poor feeding	+				+			+			
Developmental delay	+	+	+	+	-	+	+	+	+	+	+
Flat occiput	+		+	+	+						-
Bulging metopic suture		+		+							+
Arched eyebrows				+						+	-
Upward slanting eyes		+		+			+			+	
Hypertelorism					+		+		-	+	
Epicanthic folds	+	+	+	+	+	+	+	+	+	+	+
Flat nasal bridge	+	+	+	+			+			+	+
Long philtrum		-	+	+			-			+	
Micrognathia		+	+	+			+		+		+
High arched palate	+						+				+
Low set ears		+	+	+							+
Short neck	+	+		+						+	
Single palmar crease(s)	+							+	+		+
Clinodactyly		+			+		+	+	+		+
Widely spaced nipples	+	+		+							
Cardiac malformation		-		+	-			+	+	+	
Hypogonadism	-	+	+	+	+		+		+		
Foot deformities		+		+							+
Café au lait spots									+	+	
Skeletal abnormalities	+	+								+	
Joint laxity	+	+									

+ = feature present. - = feature absent. Blank = not mentioned.

The theory of Côté *et al*⁴ is supported by reports of patients who exhibit the ring syndrome and who have been shown to have complete ring chromosomes. Pezzolo *et al*¹³ showed the presence of telomeric and subtelomeric sequences in three separate patients with rings of chromosomes 4, 16, and 20 respectively, using FISH techniques. Also MacDermot *et al*¹⁴ were unable to show the loss of genetic material in three cases of ring 5, using G, R, and Q banding and scanning electron microscopy.

Our case has many similarities with previously reported cases of ring chromosome 2 (table 1). Phenotypic features shared with some or all of these include IUGR, microcephaly, postnatal growth failure, developmental delay, flat nasal bridge, epicanthic folds, café au lait spots, hypertelorism, short neck, long philtrum, arched eyebrows, mongoloid slant to the palpebral fissures, and heart defect.¹⁻⁷ Many of these dysmorphisms are relatively mild and non-specific, being associated with other chromosomal anomalies.

In our patient we were able to show a submicroscopic deletion of the 2p telomere in the ring 2 chromosome using FISH. One case, with a larger deletion of 2p (pter→p24:), has been described by Francis *et al*.¹⁵ This patient showed some overlap in phenotypic features with our ring 2 case (table 1), such as flat nasal bridge, microcephaly, growth retardation, and developmental delay. It was notable, however, that there was no IUGR, a feature common to all the cases of ring 2 reported to date (with the exception of the patient of Wyandt *et al*⁶ in whom the ring 2 was present in only 30% of cells and was accompanied by a deletion of 2q). It seems that our patient has more features in common with other cases of ring 2 than with this case of 2p deletion.

While some cases of ring chromosomes have been shown to have occurred with no accompanying deletion,^{13 14} we have shown, using FISH, that very small deletions may be present in rings which appear complete by conventional G banding. However, the ring structure itself seems to be the overriding factor in producing the phenotype of this patient. None of the previously reported cases of ring 2 have been studied using FISH so we were unable to assess the possible contribution of small deletions to the phenotype. Some of the

features, such as IUGR and growth failure, seen in patients with ring chromosomes may be the result of the ring syndrome. Other features, such as developmental delay, may be the result of aneuploidy and chromosomal imbalance caused by mitotic instability. However, they may equally be the result of deletions at the fusion point in the ring chromosome. In order to define the ring 2 phenotype accurately (or perhaps, the ring syndrome phenotype) we suggest that it is necessary to use FISH in cases of ring chromosome to distinguish between complete rings and those with a small deletion.

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