

Inheritance of a ring 14 chromosome

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SUMMARY A family is described in which the mother, her two live offspring, and a therapeutically aborted fetus each had a ring 14 chromosome. The two children were mentally retarded and the mother's intelligence was at the lower end of the normal range. In addition, the mother had two spontaneous abortions, one of which was shown to be chromosomally normal.

Since the introduction of chromosome banding techniques it has become possible to identify precisely the origin of ring chromosomes, and it would appear that a constitutional ring formed from a chromosome 14 is a rare event, in contrast to the ring 13, of which there have been numerous reports.^{1,2} In the cases of ring chromosome 14, only two have shown no obvious loss of chromosome material.^{3,4}

There are five previous published reports of inheritance of ring chromosomes, involving chromosome 17,⁵ 18,⁶ 21,⁷ 22,⁸ and a G group chromosome.⁹

This paper presents a family in which an apparently complete chromosome 14 in the form of a ring was transmitted from a mother of low-normal intelligence to two mentally subnormal children and to a fetus which was therapeutically aborted. In addition, the mother spontaneously aborted two fetuses, one of which was chromosomally normal

Case reports and cytogenetic studies

CASE II·2:46,XX,r(14)(p13q32)

The mother was the eldest of three children born when her father was aged 29 years and her mother 26 years. She had epileptic fits from shortly after birth until she was 2½ years old, but did not require special education. From the age of 21 to 27 years she had five pregnancies (fig 1).

When her second liveborn child was found to carry a ring 14 chromosome, an investigation of her chromosome constitution was undertaken. She was also found to have the ring 14, which appeared complete with no visible loss of material (figs 2a, 3a).

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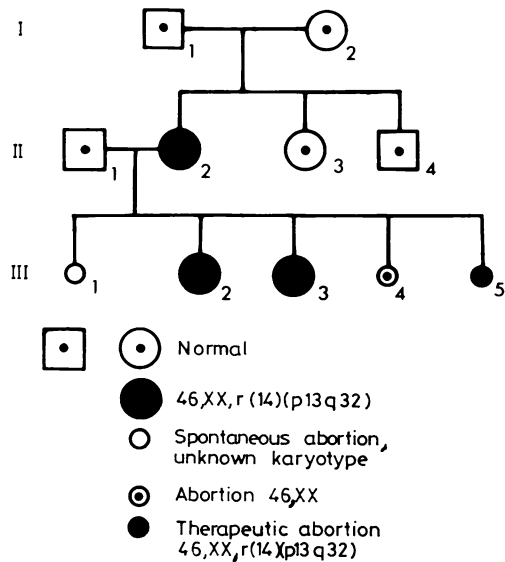


FIG 1 Family pedigree.

The karyotype description was 46,XX,r(14)(p13q32). Staining by the Bloom and Goodpasture technique¹⁰ for the nucleolus organiser regions showed that the ring had an active NOR (fig 3b).

Physical examination of the mother revealed no external abnormalities, but at laparotomy for investigation of abdominal pain an ectopic right kidney was found situated in the right iliac fossa. Her height was 168.7 cm (80th centile) and her weight 64 kg. Psychological testing using the Weschler Intelligence Scale for Adults resulted in a full scale score of 80, the performance score of 71 being significantly lower than the verbal score of 89.

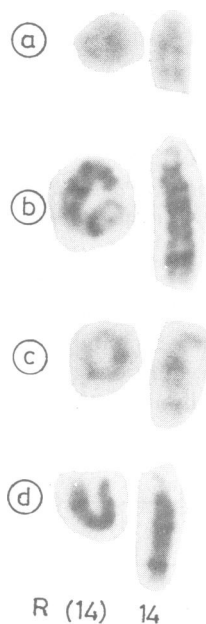


FIG 2 Chromosome 14 pair from (a) II·2, (b) III·2, (c) III·3, (d) III·5.

CASE III·2:46,XX,r(14)(p13q32)

An apparently normal healthy female infant was delivered spontaneously at term, birthweight 3·22 kg, length 50·0 cm, head circumference 34·0 cm. Physical examination was normal at 2 months of age when she was adopted. She developed normally until the age of 6 months when she had a generalised convulsion of 20 minutes' duration for which no cause was found. X-ray of the skull and an electroencephalogram showed no abnormality. Despite anti-epileptic therapy, grand mal convulsions continued and, in addition, at the age of 16 months myoclonic seizures appeared. By the age of 2½ years, regression in her developmental progress was noted with gradual loss of speech, of the ability to feed herself, and of locomotion. She was a pale microcephalic child with a vacant expression, there were involuntary movements and intention tremor of the hands, and an ataxic gait. Her optic fundi were pale but there was no cherry-red spot. Her height was between the 3rd and 10th centile. A diagnosis of degenerative brain disease was made. The following investigations gave normal results: x-ray of chest, skull, and wrist; urinary amino-acid chromatogram; blood and urine lead levels; serum B₁₂ and folate levels; cerebrospinal fluid protein and measles antibody titre; gangliosides in blood and fibroblasts; examina-

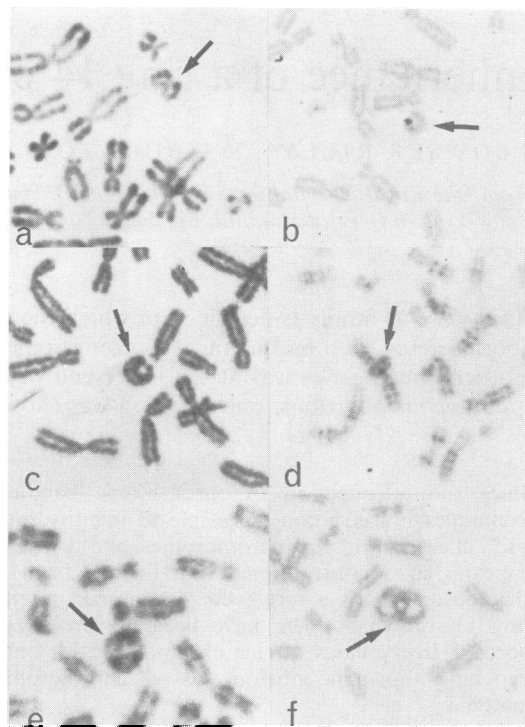


FIG 3 Part of 6 cells showing the ring 14. (a) R banded; (b) Ag stained, with an active NOR region; (c) conventionally stained with the stalk region in association with a D group chromosome; (d) G banded with the ring around a chromosome 2; (e) G band: a double ring; (f) conventionally stained two dicentric rings interlocked.

tion of lymphocytes for foamy changes; toxoplasma antibody titre and blood thyroxine level. Her electroencephalogram was abnormal and showed irregular slow and theta waves of fairly large amplitude with occasional spike potentials. This was interpreted as evidence of generalised cerebral abnormality without striking epileptic features. The clinical assessment was that her IQ was below 50.

Chromosomes were examined in the RHSC laboratory using peripheral blood and skin cultures and most cells showed a 46,XX,r(14)(p13q32) karyotype (fig 2b). The ring was lost from 13% of the peripheral blood cells analysed (table). In the majority of G banded cells, the ring appeared 'open' because of the presence of a long satellite stalk which was not staining. Satellite association with the 'stalk' region of the ring was clearly visible (fig 3c). As in the mother, a complete chromosome 14 appeared to make up the ring.

TABLE Distribution of the ring types between cells

Family member	Tissue	Age at blood culture	Length of culture time	No of cells					Total
				46,XX monocentric ring	46,XX dicentric ring	47,XX 2 rings	45,XX no ring	46,XX 'normal'	
II·2	Blood	26 yr	3 d	87	1	2*	9	1	100
III·2	Blood	2½ yr	3 d	85	1	1	13	0	100
	Skin	—	—	27	0	0	2	1	30
III·3	Blood	6 d	2 d	29	0	0	0	1	30
	Blood	1 mth	3 d	89	4	2†	3	2	100
III·5	Amniotic fluid	—	—	50	1	0	9	0	60

*One cell had two dicentric rings interlocked (see fig 3f).

†One cell had one r(14) and two 'normal' chromosomes 14.

CASE III·3:46,XX,r(14)(p13q32)

This child was delivered by the breech with forceps to the aftercoming head after being converted from a transverse lie. The infant, a female, had a birthweight of 3·30 kg, a length of 50·7 cm, and a head circumference of 33·8 cm (20th centile). She failed to breathe spontaneously and required intermittent positive pressure respiration by endotracheal tube for 5 minutes. During the next few days her muscle tone remained poor and she fed with difficulty. In view of this, chromosome analysis was carried out by the MRC laboratory from a peripheral blood culture and the child was found to have the karyotype 46,XX,r(14)(p13q32). Again there appeared to be no loss of chromosome 14 material in the formation of the ring (fig 2c). Her initial progress on follow-up was reasonably good but at the age of 8 months she was admitted to hospital with prolonged grand-mal convulsions. She was mildly pyrexial and was found to have an *E coli* type O55 infection of the bowel. Prolonged convulsions continued in hospital and were difficult to control medically. Further investigation included an electroencephalogram which showed loss of activity in the right frontal area, and computerised tomography which revealed cortical atrophy in the same area with a degree of hydrocephalus.

Assessment at 3 years and 3 months of age showed an obese ataxic child, without any congenital malformations, weight 24·0 kg, height 98·9 cm, (80th centile), and head circumference 48·9 cm (10th centile). Psychometric evaluation showed her expressive speech to be at a 15 to 18 month level, while her verbal comprehension and fine and gross motor development were all at an 18 month level. The overall assessment of her cognitive development suggested an IQ of approximately 50.

CASE III·4

This was a missed abortion. The karyotype was found by the RHSC laboratory to be 46,XX from amniotic

fluid cell culture. The products of conception consisted of a degenerate ruptured gestational sac approximately 7 cm in diameter which contained neither cord nor fetus.

CASE III·5

Therapeutic termination of pregnancy was carried out because the fetal chromosome complement was found by the RHSC laboratory to be 46,XX,r(14) from amniotic fluid cell culture. Necropsy by Dr A Patrick showed a morphologically normal fetus apart from rudimentary development of one of the two umbilical arteries.

The mother's parents (I·1 and I·2), her sister (II·3), brother (II·4), and husband (II·1) had normal karyotypes.

Examination of the polymorphic Q bands on the short arm of chromosome 14 gave no information as to which of the parent's chromosomes 14 had resulted in the ring 14 in case II·2. Blood groups and genetic enzyme marker studies were carried out on I·1, I·2, II·2, II·3, II·4, and III·3, and there being no blood group incompatibilities between II·2 and her parents, it was concluded that the ring chromosome must be a de novo structural rearrangement.

Discussion

Ring chromosomes are an infrequent constitutional abnormality and in most reported cases result in a deleterious effect on somatic and brain development.

Ring 13 chromosomes have been reported frequently and are associated both with multiple external malformations of a fairly characteristic pattern and with mental retardation.^{1 2}

Ring 14 chromosomes have been described by three groups of authors.^{3 4 11} All four patients were female and were severely mentally retarded, although in the case of the monozygotic twins of Jalbert *et al*³ their premature birth may have contributed to their retardation. These twins showed no

congenital malformations and in this were similar to our four cases. It is worth commenting on the fact that our four cases were all females, and that so far no case of ring 14 chromosome has been reported in a male.

The mother (II·2) is interesting in that she is not retarded and, but for the abnormal findings in her children, may have remained undiagnosed. Rings derived from other chromosomes have been reported in subjects with normal intelligence. For example Surana *et al*¹² described a patient with a ring 4 chromosome, normal intelligence, and short stature, and two further patients with the same chromosome abnormality and borderline normal intelligence have also been reported.^{13 14} In the two reports of ring 15 chromosome,^{15 16} there was only slight mental retardation with short stature.

It would appear therefore that one cannot predict with certainty that severe mental retardation will be associated with the presence of a ring chromosome. There may have been additional cerebral insults in a number of cases, for example, in our case III·3 there was a possibility of cerebral trauma from the breech delivery.

While it is interesting to speculate that there may be other cases in the population as minimally affected as case II·2, it should be noted that no cases with ring chromosome abnormalities were detected in the numerous newborn chromosome surveys which have now screened 64 860 infants, thus confirming the rarity of ring chromosomes in the general population. (The case originally reported¹⁷ with a mosaic ring constitution was later demonstrated on fluorescence and banding to have a marker chromosome.)

Short stature, microcephaly, and low birthweight are frequently associated with ring 13 chromosome but are not a feature in the ring 14 cases. Two of our three surviving cases were of above average height. The cases of Abe *et al*⁴ and Gilgenkrantz *et al*¹¹ were described as being of normal height, weight, and head circumference, while the premature twins of Jalbert *et al*³ with birthweights of 1·48 kg and 1·92 kg reached the 15th centile for height by the age of 3 years.

Turning to the effect of the presence of ring chromosomes on fertility, it is clear from our family that in the female, fertility was not impaired whereas, in the male, ring chromosomes have been reported to cause sterility through spermatogenic impairment.^{18 19} In these cases meiotic studies showed failure of pairing between the ring chromosome and its normal homologue. However, Burden *et al*⁵ describe the transmission of a ring 17 chromosome from father to son. In the case described by Palmer *et al*⁷ of inheritance of a ring 21 there was simultaneous

appearance in the child of an extra X chromosome which the authors believed to be a related phenomenon. They suggested that a 'distributive pairing' mechanism²⁰ might have operated at meiosis in the mother to produce the two abnormalities in the child. In cases where the offspring is more severely affected than the parent, it may be that further minute but undetectable loss of chromosome material has occurred during the exchange events at meiosis in the parent.

The finding of monozygotic twinning in two of the reports of subjects with ring chromosomes^{3 21} is a surprising concurrence of two rare events, and the association may not be fortuitous.

A ring chromosome is essentially an unstable rearrangement, because the two chromatids will frequently become interlocked at anaphase, one result of which is chromatid breakage and reunion to form a dicentric ring. Alternatively anaphase lagging may occur leading to non-disjunction of the ring. In most, if not all, subjects carrying a ring chromosome, the ring is absent, duplicated, or dicentric in a small number of cells. In the r(14) carriers from our family, all these changes were seen (table, fig 3). The 45,XX, -r(14) cells occurred more frequently in cells cultured for 3 days, when the majority of cells will have gone through at least one division *in vitro*. It is probable therefore that loss of the ring is a 'culture effect'; it is doubtful whether a cell would be able to withstand monosomy 14 *in vivo*. Another cause of non-disjunction may have been that in a proportion of cells the ring became threaded through by another chromosome, usually one of the A group chromosomes (fig 3c).

The apparent completeness and the 'open' shape of the ring 14s found in this family have also been observed by others.^{3 4} The 'open' shape was the result of a long 'stalk' region (band p12), which contained an active NOR and associated readily with other D and G group chromosomes. This ability to associate in a slightly unconventional way, or the problems caused by chromatid interlocking during division of the ring, or both, may have resulted in the increased mitotic non-disjunction in the cells of all the subjects carrying the ring, whom we consider are not true mosaics, but are constitutionally 46,XX,r(14)(p13q32) with a high number of aneuploid cells.

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